Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Fosfomycin trometamol

Proprietary Product Name: Monurol

Sponsor: Mayne Pharma International Pty Ltd

First round: November 2016

Second round : May 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADR	Adverse drug reaction
AGAR	Australian Group on Antimicrobial Resistance
AE	Adverse event
ARESC	Antimicrobial Resistance Epidemiological Survey on Cystitis
AUC_{24h}	Area under the concentration-time curve at 24 h
AURA	Antimicrobial Use and Resistance in Australia
Ccr	Creatinine clearance
CFU/mL	Colony forming units per millilitre
CLSI	Clinical and Laboratory Standards Institute
C_{max}	Maximum concentration or peak
C_{min}	Minimum concentration or trough
ESBL	Extended spectrum betalactamase-producing
ESCAPPM	Enterobacter, Serratia, Citrobacter, Aeromonas, Proteus vulgaris, Providencia, Morganella species
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDIU	Fetal death in utero
FT	Fosfomycin
G6PD	Glucose-6-phosphate dehydrogenase
IDSA	Infectious Diseases Society of America
INR	International normalised ratio
ITT	Intention to treat
MIC	Minimum inhibitory concentration
MITT	Modified intention to treat
MRSA	Methicillin-resistant Staphylococcus aureus

Abbreviation	Meaning
MSSA	Methicillin-susceptible Staphylococcus aureus
NCCLS	National Committee for Clinical Laboratory Standards
NF	Nitrofurantoin
PD	Pharmacodynamic
PI	Product Information
PK	Pharmacokinetic
RMP	Risk management plan
SAE	Severe or serious adverse event
SAS	Special Access Scheme
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
spp.	Species
$T_{1/2}$	Half-life
T_{max}	The amount of time that a drug is present at the maximum concentration in serum
TMP / SMX	Trimethoprim / sulfamethoxazole
UTI	Urinary tract infection
VRE	Vancomycin-resistant enterococci
VSE	Vancomycin-susceptible enterococci

1. Introduction

1.1. Submission type

This is a submission to register a new chemical entity Fosfomycin trometamol. It is a full submission with 3 pivotal efficacy studies (meeting good clinical practice guidelines) and a very large number of nonpivotal studies.

1.2. Drug class and therapeutic indication

Fosfomycin is a low molecular weight phosphonic acid derivative which has a unique mechanism of action inhibiting the first stage of peptidoglycan synthesis in the bacterial cell wall. It was first isolated naturally from *Streptomyces fradiae* in 1969 by MSD but is now mostly obtained synthetically. When given orally, fosfomycin is combined with either a calcium or tromethamine salt for improved bioavailability. Fosfomycin trometamol (Monurol™) has better oral bioavailability than either fosfomycin calcium or fosfomycin alone.

Fosfomycin trometamol has rapid bactericidal activity and a wide antibacterial spectrum including methicillin-resistant *Staphylococcus aureus,* enterococci and Gram negative bacilli including *Pseudomonas* spp. and many extended spectrum beta-lactamase (ESBL)-producing Gram negatives.

Fosfomycin trometamol (Monurol) 3g oral sachets are available in Australia under the Special Access Scheme (SAS). The most common indication for use of the drug under the SAS scheme is for oral treatment of urosepsis, particularly the treatment of multiresistant Gram negative bacteria. To the best of my knowledge, the drug has never been submitted to the TGA for approval in Australia.

Fosfomycin is the only antibacterial agent in its class and acts at a different stage of cell wall synthesis than the beta-lactam antibiotics such as penicillins and cephalosporins. This means that cross-resistance with other antibiotics is unlikely.

There are two proposed indications in this submission for fosfomycin trometamol. The first is the treatment of uncomplicated lower urinary tract infections caused by pathogens sensitive to fosfomycin in women above 12 years of age. The second proposed indication is prophylaxis of urinary tract infections in surgical or diagnostic procedures involving the lower urinary tract in adult males and females. Note that children less than 12 years of age are excluded from both indications, and male sex is an exclusion criteria for the first treatment indication. The draft PI also states:

> *The use of Monurol may be considered during pregnancy, if necessary.*

1.3. Dosage forms and strengths

The submission proposes registration of one dosage form and strength. This is the 3g fosfomycin trometamol Monurol sachet presented as white granules for oral solution.

1.4. Dosage and administration

The recommended dose for the proposed treatment indication of acute uncomplicated lower urinary tract infections is a single Monurol 3 g sachet in women above 12 years of age.

The recommended regimen for the proposed prophylaxis regimen of prophylaxis of urinary tract infections in surgery and diagnostic procedures involving the lower urinary tract in adult males and females is one Monurol 3 g sachet 3 hours before surgery and one Monurol 3 g sachet 24 hours after surgery.

It should be taken on an empty stomach or about 2 – 3 hours after meals, preferably before bedtime and after emptying the bladder. The dose should be dissolved into a glass of water and taken immediately after its preparation.

1.5. Information on the condition being treated or requiring prophylaxis

1.5.1. Proposed indication 1: Treatment of acute uncomplicated lower urinary tract infections in women above 12 years of age.

Symptomatic urinary tract infections (UTI) are a very common disease, with particularly high incidence in women of child-bearing age. These infections occur in 1 to 3% of schoolgirls then increase markedly in incidence with the onset of sexual activity in adolescence. Symptomatic UTI is very common in women aged 20-50 years, but it is rare in men under 50 years. UTIs are usually classified as either complicated or uncomplicated. The diagnosis of uncomplicated UTI is made if there is no evidence of pyelonephritis or upper UTI, no renal or urological abnormalities, no urinary retention or urinary catheter. Acute uncomplicated lower UTI (also known as cystitis) is extremely common, being estimated to occur in about 6% of adult women per year.

Escherichia coli causes 70-95% and *Staphylococcus saphrophyticus* 5-10% of episodes of acute uncomplicated cystitis (Therapeutic Guidelines Antibiotic 2014). In older females especially those who have been hospitalised or resident in other healthcare facilities, *Staphylococcus saphrophyticus* (which is primarily sexually acquired in young women)becomes less common and other Gram negative bacilli such as *Proteus, Klebsiella, Enterobacter* and P*seudomonas* spp. become more common.

1.5.2. Proposed indication 2: Prophylaxis of urinary tract infections in surgery and diagnostic procedures involving the lower urinary tract in adult males and females

In surgery and diagnostic procedures involving the urinary tract, the need for surgical antibiotic prophylaxis, as well as antibiotic choice, depends on: the surgical approach (endoscopic, open or laparoscopic); whether the urinary tract is manipulated; patient-specific risk factors (eg immunocompromise, urinary tract obstruction or abnormalities, urinary stones, indwelling or externalised catheters); use of prosthetic material; and whether entry into the gastrointestinal tract is likely (Therapeutic Guidelines Antibiotic 2014).

Routine surgical antibiotic is recommended in transrectal prostatic biopsy and in prostatectomy. There is a low risk of postoperative infection following uncomplicated cystoscopic diagnostic procedures. In patients with sterile urine, antibiotic prophylaxis is not recommended for diagnostic cystoscopy without other manipulation of the urinary tract. Prophylaxis is indicated for endoscopic intrarenal and ureteric stone procedures (eg percutaneous nephrolithotomy, ureteroscopy or pyeloscopy for ureteric or renal stones). Prophylaxis should be considered for any endoscopic procedure if there are specific risks for postoperative infection (eg resection of large or necrotic tumours, risk of bleeding, bladder outlet obstruction with incomplete bladder emptying) (Therapeutic Guidelines Antibiotic 2014).

1.6. Current treatment options prophylaxis options

1.6.1. Proposed indication 1: Treatment of acute uncomplicated lower urinary tract infections in women above 12 years of age

First-line therapy for acute uncomplicated cystitis in nonpregnant women is trimethoprim, cephalexin, amoxicillin-clavulanate or nitrofurantoin. In pregnancy, trimethoprim is contra-indicated, but trimethoprim (pregnancy category A), cephalexin (pregnancy category A), amoxicillin-clavulanate (pregnancy category B1), may be used (Therapeutic Guidelines Antibiotic 2014).

In patients who have been hospitalised and/ or have received multiple courses of antibiotics, urinary tract pathogens become resistant to the first-line antibiotics mentioned above. Patients then require antibiotics such as cotrimoxazole or fluoroquinolones (usually norfloxacin or ciprofloxacin). These isolates may carry extended spectrum beta-lactamases (ESBLs) and/or inducible beta-lactamases and hence may be resistant to most or all beta-lactam antibiotics. Isolates which carry ESBLs (usually *Klebsiella, E coli* or *Enterobacter*) and / or inducible beta-lactamases (the ESCAPPM group of Gram negative bacilli) are frequently also resistant to other antibiotic groups such as fluoroquinolones and sulphamethoxazole. In these patients, a novel agent such as fosfomycin would be an ideal therapeutic agent with prior resistance unlikely as it is the first agent of its class in Australia and acts at a different site to other antimicrobials currently available in Australia. Additionally, it would be a useful oral therapeutic alternative in patients with *Pseudomonas* cystitis with fluoroquinolone resistance or intolerance or other contraindications. Currently, fluoroquinolones are the only oral therapy available in Australia for *Pseudomonas* urosepsis so an alternative therapy such as fosfomycin would be welcome.

1.6.2. Proposed indication 2: Prophylaxis of urinary tract infections in surgery and diagnostic procedures involving the lower urinary tract in adult males and females

Currently, there are only two urological surgery procedures in Australia in which antibiotic prophylaxis is recommended routinely. These are single dose gentamicin (unless contraindicated) in prostatectomy, which gentamicin prophylaxis has been shown to reduce the incidence of post-operative bacteremia. The second surgical procedure is transrectal prostatic biopsy, where ciprofloxacin 500m mg orally as a single dose has been shown to be of benefit (Therapeutic Guidelines Antibiotic 2014). Ciprofloxacin has much better penetration into prostatic tissue than many other antibiotics such as beta-lactams. If urine is sterile pre-operatively, there are no other urological surgery procedures which routinely require surgical antibiotic prophylaxis.

Gentamicin resistance is rare in Australia in prostatectomy patients. However, gentamicin is contraindicated in patients with moderate to severe renal impairment and / or issues with hearing or the vestibular system. These patients require an alternative antimicrobial agent prior to prostatectomy. An alternative agent would be clinically useful.

Ciprofloxacin resistance was rare in patients undergoing transrectal prostatic biopsy until recently. Urinary tract pathogens and bowel flora in Australia have much lower rates of ciprofloxacin resistance compared to Southeast Asia and elsewhere in the world. This is likely partly due to the tight restrictions on fluoroquinolone usage in Australia compared to other countries. However, some ciprofloxacin resistance is now seen especially in patients from SouthEast Asia countries. Some patients cannot be given ciprofloxacin due to potential interactions with drugs such as oral hypoglycemics, cyclosporin, phenytoin, and theophylline or because of pre-existing adverse events with fluoroquinolones such as Achilles tendonitis. Again, an alternative agent would be clinically useful.

1.7. Clinical rationale

Symptomatic urinary tract infections (UTI) are a very common disease, with particularly high incidence in women of child-bearing age. These infections occur in 1 to 3% of schoolgirls and then increase markedly in incidence with the onset of sexual activity in adolescence. Symptomatic UTI is very common in women aged 20-50 years, but it is rare in men under 50 years. UTIs are usually classified as either complicated or uncomplicated. The diagnosis of uncomplicated UTI is made if there is no evidence of pyelonephritis or upper UTI, no renal or urological abnormalities, no urinary retention or urinary catheter. The most common organisms causing uncomplicated UTI are *Escherichia coli, Proteus species, Klebsiella pneumoniae*, other Enterobacteriaceae and *Staphylococcus saprophyticus.* Acute uncomplicated lower UTI is extremely common, being estimated to occur in about 6% of adult women per year.

Most uncomplicated UTIs respond well to oral antimicrobial treatment when the appropriate compounds are taken as directed. Traditionally, treatment duration was of 5-10 days, but there has been a noticeable trend towards shorter courses (three days or less) in recent years. With a multi-day antibiotic regimen, poor compliance, favored by the rapid resolution of clinical symptoms, is well documented. Response to therapy may be compromised in non-compliant patients, and this noncompliance may be, in part responsible for increasing bacterial resistance.

A single-dose antibiotic that is both safe and effective would, therefore, be a significant therapeutic advance in the treatment of uncomplicated UTI, since it would increase patient convenience, enhance compliance, minimize adverse events, and reduce the potential for selection of antibiotic resistant bacteria.

Fosfomycin is currently being used to treat multi-resistant isolates such as these on the SAS scheme in Australia. It is active against the most common urinary pathogens involved in uncomplicated UTI. It appears to have no cross-resistance with other antibiotic agents as it is the first and only agent in its class. It also appears to have few adverse effects.

Additionally fosfomycin is a potentially useful therapy for uropathogens which carry resistance genes such as ESBLs or inducible-betalactamases (ESCAPPM Gram negative bacilli). These isolates may be resistant to all other oral antibiotics available in Australia. It also may have activity against carbapenem-resistant *Enterobacteriaceae* and carbapenem-resistant non-fermentative Gram negative bacilli such as *Pseudomonas* (Pulcini et al, 2012).

Fosfomycin has been included in a list of 33 “forgotten antibiotics” drawn up by infectious diseases specialists, microbiologists and hospital pharmacists in 38 countries from Europe, United States, Canada and Australia. Fosfomycin has been included on the list with 2 particular qualities highlighted: (1) that it is the only available antibiotic of its class, and (2) for its favourable pharmacokinetic criterion of requiring only 1 dose to treat uncomplicated cystitis. Another favourable quality its potential to treat infections caused by carbapenem-resistant Gram negative bacilli (Pulcini C 2012).

The clinical rationale for the proposed introduction into the Australian market is to improve and broaden the therapeutic options for the treatment of acute uncomplicated lower UTI in adult females. The second proposed indication aims to improve and broaden the prophylaxis options for urinary tract infections in surgery and diagnostic procedures involving the lower urinary tract in adult males and females.

1.8. Guidance

Pre-submission advice from the TGA was that the sponsor should submit a conventional dossier. No pre-submission meeting was required or held. TGA have also advised the sponsor that the two flavouring agents are already in use in other oral medicines and as such have already been approved by the TGA. The sponsor has advised TGA that microbial resistance risk

will be based on overseas resistance data due to lack of local Australian data, with this data to be generated in the future. I would agree that this is likely to be the case.

1.9. Evaluator's commentary on the background information

Background information appears correct and appropriate. Sufficient information has been provided on clinical rationale, formulation and its development and regulatory history.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Three pivotal efficacy/safety studies: MON-US-01, MON-US-02, and MON-US-03.
- Eight clinical pharmacology studies providing PK data.
- Seventeen other efficacy/safety studies.
- Nine periodic safety update reports (PSURs) covering the period from Jan 1995-Jan 2016.
- There were no good dose-finding studies.
- 76 Literature references. These were composed of review articles, background information, PK and PD studies, and other efficacy/safety studies.
- All studies for the proposed 5 prophylaxis indication were contained in "Literature references". These therefore required detailed review but none are considered pivotal and they also did not meet GCP principles.
- One meta-analysis[1]
- 18 PK studies providing supporting data.
- All the PD data in the dossier, 4 studies only.
- 9 studies which included pregnant women. These required detailed review especially for safety in pregnancy.
- There were no studies which included lactating women.
- The following efficacy/safety studies in special populations: the elderly, 2 studies; chronic renal impairment 1 study, ESBL-producing bacteria or fosfomycin-resistant bacteria, 4 studies.
- 4 good review publications and 2 papers providing background microbiology information.

2.2. Paediatric data

A paediatric indication was not requested. The age group requested for the first indication is females 12 years or older. Sufficient data has been provided in the dossier for this age group.

[1] Falagas ME, et al. Fosfomycin. Clin Microbiol Rev. 2016 Apr;29(2):321-47.

2.3. Good clinical practice

Only the 3 pivotal efficacy and safety studies MON-US-01, MON-US-02 and MON-US-03 meet the principles of GCP. The other studies in the submission were mostly conducted prior to the adoption of GCP principles. Despite this, as a group, they provide useful and relevant information.

2.4. Evaluator's commentary on the clinical dossier

The submission was generally well-presented.

3. Pharmacokinetics

3.1.1. Studies providing pharmacokinetic information

Below shows the studies relating to each PK topic.

Table 1: Submitted pharmacokinetic studies

PK topic	Subtopic		Study ID	*
PK in healthy adults	General PK	- Single dose	Kisicki 1994[2]	
			Borgia 1982[3]	*
			Borgia 1984[4]	*
			Thorsteinsson 1992[5]	*
		- Multi-dose	Not provided	
	Bioequivalence †	- Single dose	Not provided	
		- Multi-dose	Not provided	
	Food effect		Kisicki 1994[6]	*
PK in special populations	Target population §	- Single dose	Not provided	
		- Multi-dose	Not provided	
	Hepatic impairment		Not provided	

[2] Study objectives: 1. To determine the absolute bioavailability of oral fosfomycin tromethamine and to evaluate the effect of food on oral absorption. 2. To evaluate a new microbiologic assay of fosfomycin.
[3] Study objectives: To evaluate serum concentrations and antibiotic urinary recovery after an oral 3g dose of fosfomycin trometamol.
[4] Study objectives: To assess the oral bioavailability of calcium fosfomycin in healthy volunteers and compare it to the bioavailability of trometamol fosfomycin (FZ588 or Monuril)
[5] Study objectives: To compare the PK parameters of a single oral administration of different doses of fosfomycin trometamol (FZ588) with those of a single intraveous injection of fosfomcyin disodium salt and to evaluate the bioavailability.
[6] Study objectives: 1. To determine the absolute bioavailability of oral fosfomycin tromethamine and to evaluate the effect of food on oral absorption. 2. To evaluate a new microbiologic assay of fosfomycin.

PK topic	Subtopic	Study ID	*
	Renal impairment	Fillastre 1988[7]	*
	Neonates / infants / children / adolescents	Careddu 1987[8]	*
	Elderly	Fillastre 1988[9] Salvioli 1985[10] Janknegt 1994[11]	 * *
	Pregnancy	De Cecco 1987[12]	
Genetic/gender related PK	Males versus females	yes	
	Other genetic variable	Not provided	
PK interactions	Metoclopramide	Bergan 1988[13]	*
	Cimetidine	Bergan 1988[14]	*
Population PK analyses	Healthy subjects	Not provided	
	Target population	Not provided	
	Other	Not provided	
Tissue distribution	Prostate	Moroni 1984[15]	
	Bladder tissue	Scaglione 1994[16]	
	Placenta	Ferreres 1977[17]	

* Indicates the primary PK aim of the study.

None of the studies had deficiencies that excluded their results from consideration. Some studies compared fosfomycin trometamol with the less bioavailable calcium fosfomycin salt which has an inferior PK profile to fosfomycin trometamol. In the study summaries, the evaluator has chosen to focus on the PK of fosfomycin trometamol, as it is the formulation proposed by the sponsor.

[7] Study objectives: To compare the PK of fosfomycin trometamol in elderly subjects and uraemic patients.
[8] Study objectives: To assess the PK of fosfomycin trometamol in children on treatment with fosfomycin for UTI.
[9] Study objectives: To compare the PK of fosfomycin trometamol in elderly subjects and uraemic patients.
[10] Study objectives: To evaluate pharmacokinetics and bioavailability after an oral 3g dose of fosfomycin trometamol (Z1282 or Monuril) in elderly hospitalised patients.
[11] Study objectives: To assess the PK of fosfomycin trometamol in elderly patients with impaired renal function.
[12] Study objectives: To investigate the PK of fosfomycin trometamol during pregnancy.
[13] Study objectives: To investigate any PK interaction of fosfomycin with metoclopramide and cimetidine.
[14] Study objectives: To investigate any PK interaction of fosfomycin with metoclopramide and cimetidine.
[15] Study objectives: To investigate tissue distribution of fosfomycin into the prostate.
[16] Study objectives: To investigate tissue distribution of fosfomycin into the bladder mucosa.
[17] Study objectives: To evaluate the placental transfer of fosfomycin trometamol.

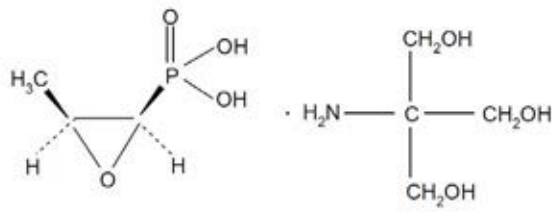
3.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional PK studies in humans unless otherwise stated. Due to the number of studies included in this evaluation, discussion of the studies in this section has primarily centred on the proposed dose as identified in the proposed product information ie a single oral 3g fosfomycin trometamol (Monurol) sachet.

3.2.1. Physicochemical characteristics of the active substance

Fosfomycin trometamol is also known as fosfomycin tromethamine in the United States. It is a water-soluble salt of fosfomycin synthesised to improve the oral bioavailability of fosfomycin.

Figure 1: Chemical structure of fosfomycin trometamol



Empirical formula:	C7H18NO7P
Chemical name:	2-hydroxy-1,1-bis(hydroxymethyl)ethylammonium(2R,3S)-(3 methyloxiran-2-yl) phosphonate
Laboratory code:	Z1282
Molecular weight (g/mol):	259.2
Physical state:	White or nearly white crystalline powder very soluble in water. It is slightly soluble in 95% methanol and ethanol, almost insoluble in anhydrous acetone, in ether and in chlorinated solvents.
pKa:	2.5 and 6.7
Optical isomerism:	Specific optical rotation between -13.5 and -12.5.

3.2.1. Pharmacokinetics in healthy subjects

3.2.1.1. Absorption

Sites and mechanisms of absorption

The drug is dissolved into a glass of water and taken immediately after preparation. Oral fosfomycin trometamol is rapidly absorbed in the gut and converted to fosfomycin.

3.2.1.2. Bioavailability

Absolute bioavailability

The absolute bioavailability of a Monurol sachet containing fosfomycin trometamol equivalent to 3g active fosfomycin in healthy adult volunteers was 37% in fasting states (n=24)(Kisicki 1994), 46% +/- 2% (n=5) (Borgia, 1984) and 32.88 +/- 7.96 % (n=12) (Thornsteinsson 1992).

Bioequivalence of clinical trial and market formulations

The majority of the PK studies in the dossier utilised the 3g oral fosfomycin trometamol sachet proposed for marketing. PK studies were conducted in healthy adult volunteers and used a single dose of 3g oral Monuril or Monurol fosfomycin trometamol sachet marketed by Zambon. This is the current formulation proposed for marketing in Australia with a change to the one flavouring agent only. The early study listed by Borgia 1982 utilised a three 1g sachets given together. Some studies incorporated lower oral dosages, IV dosages of fosfomycin and/ or the effect of food.

The PK parameters after a single 3g oral dose of fosfomycin trometamol in adult volunteers are summarised in the table below:

Table 2: Mean PK parameters after 3g oral fosfomycin trometamol in fasting healthy adult volunteers

Study	C_{max} (ug/ml)	AUC_{24}(ug.h/ml)	T_{max} (hr)
Kisicki 1994	26.1	184	2.1
Borgia 1982	20.9	120.4	2.3
Borgia 1984	32.0	150.9	2.0
Thorsteinsson 1992	21.8	144.9	2.0

Oral fosfomycin trometamol is rapidly absorbed and converted to fosfomycin. A mean Cmax of 20.9–32.0 µg/mL was reached within about 2 h following administration of a single dose of fosfomycin trometamol 3 g under fasting conditions.

Bioequivalence of different dosage forms and strengths

Only a single dosage form and strength is proposed for the -to-be-marketed formulation of fosfomycin trometamol.

Bioequivalence to relevant registered products

Not applicable.

Influence of food

A high fat breakfast reduced the bioavailability of fosfomycin trometamol from 37% to 30% (Kisicki, 1994). In this study, food decreased the rate and extent of absorption. In the study by Thornsteinsson and Bergan, bioavailability was 32% in patients given breakfast immediately after the dose.

Dose proportionality

The majority of the PK studies utilised the 3g oral fosfomycin trometamol sachet. The study by Thorsteinsson 1992 examined a 2g, 3g and 4g dose. Mean Cmax values in serum were proportionate to dose and were 16.0 ± 4.4 µg/ml, 21.8 ± 4.8 µg/ml and 30.8 ± 5.6 µg/ml after 2, 3 and 4 g fosfomycin, respectively. AUC was proportionate to oral dosage with mean AUC_{0-12} values were 106.6 ± 34.9 µg.h/ml, 144.9 ± 40.5 µg.h/ml and 189.8 ± 50.1 µg.h/ml, respectively. Tmax were about 2 hours and serum t½ were about 4 hours at all doses. Bioavailability was 30-35% for all dosages. The proportion of the administered doses recovered in the urine over 72 hours were similar at 38.2 ± 10.5, 39.1 ± 6.7 and 39.8 ± 3.7 for the three doses, respectively.

Bioavailability during multiple-dosing

The dossier did not include any PK information for multiple-dosing of fosfomycin. The sponsor has requested a single 3g oral dose only.

Comment: There appears to be a very limited amount of data for the PK of multiple doses of fosfomycin, for example in the treatment of complicated UTI. Typical dosage regimens in complicated UTI have been 3g sachet every 48-72 hours but minimal if any PK data exists for these regimens.

Effect of administration timing

There were no studies in the dossier which assessed the effect of varying dose time on bioavailability e.g. morning versus evening dosing.

3.2.1.3. Distribution

Volume of distribution

The apparent volume of distribution of fosfomycin trometamol in healthy volunteers was about 16-21 litres, approximately the size of the extracellular fluid compartment indicating that the drug distributes widely into extra-vascular compartment (Thorsteinsson and Bergan, 1992).

Plasma protein binding

In a study of 10 healthy volunteers, plasma protein binding was 0% (Kestle and Kirby, 1969). No other studies were presented.

Erythrocyte distribution

No data presented.

Tissue distribution: Prostate

Fosfomycin has good penetration into the prostate. In the study by Moroni (1984), 6 patients undergoing prostatectomy for adenoma had samples of prostate tissue and sera collected at the same time sent for fosfomycin levels. Patients were fasting overnight and received 3g Monuril sachet 3 hours before prostatectomy. Penetration of fosfomycin into the prostate ranged from 57-100% of serum levels (mean 90%).

Tissue distribution: Bladder tissue and urine

In the study by Scaglione (1994), 30 adults with prostatic or bladder carcinoma had serum and bladder mucosa samples collected at the same time after 3g single dose fosfomycin. Peak concentrations were detected 3-6 hours after dosing in serum and bladder mucosa. In serum, fosfomycin was detectable until the 24th hour and in bladder mucosa until the 36th hour. Bladder mucosa fosfomycin concentrations attained values higher than the MICs of the most common urinary tract pathogens for at least 36 hours. In urine, fosfomycin concentrations were markedly higher than those found in serum and bladder mucosa, with maximal values reached within 3 hours post dosing. Urine concentrations of fosfomycin were also at antibacterial levels at the study end (48 hours).

Tissue distribution: Placenta

Fosfomycin penetrates the placenta resulting in high drug levels in fetal blood. In the study by Ferreres (1977), the placental transfer of fosfomycin was assessed. Ten pregnant women in labour had fosfomycin concentrations monitored. Each mother received 1g of fosfomycin sodium salt intramuscularly at onset of labour. By 120-210 minutes after dosing, concentrations of fosfomycin in fetal blood were a mean of 68% of maternal levels. There was a clear correlation between heavier weight of placenta and higher fosfomycin concentration.

Comment: There are no studies of placental transfer of the oral formulations but as the parenteral and oral formulations convert to fosfomycin active drug, presumably the oral formulation also has high placental transfer although the PK of this is unknown.

Tissue distribution: Seminal vesicles

The proposed Product Information states "Fosfomycin is distributed to the… seminal vesicles". A study by Chezzi et al (1989) claims to show that the drug penetrates seminal vesicles. However, the listing of Chezzi et al (1989) has an abstract only without any data or results.

Comment: Could the sponsor provide the full publication or poster by Chezzi et al (1989) to allow full evaluation of penetration of the drug into seminal vesicles.

3.2.1.4. Metabolism

Interconversion between enantiomers

Not applicable.

Sites of metabolism and mechanisms / enzyme systems involved

Fosfomycin does not undergo metabolism and is primarily excreted unchanged in the urine (Bergan 1995).

Non-renal clearance

Non-renal clearance is negligible, since total body and renal clearances are similar.

Metabolites identified in humans: active and other

Fosfomycin does not undero metabolism so there are no metabolites.

Pharmacokinetics of metabolites

Fosfomycin does not undero metabolism so there are no metabolites.

Consequences of genetic polymorphism

No data presented.

3.2.1.5. Excretion

Renal clearance and urinary excretion

Total body clearance and renal clearance are similar so non-renal clearance is thought to be negligible. Total clearance of fosfomycin corresponds closely to the glomerular filtration rate, so neither tubular secretion nor reabsorption are thought to occur (Kestle 1969; Patel, 1997). In general, up to 40% of an orally administered dose of fosfomycin tromethamine is excreted renally within 48 hours and, of this, approximately 85 to 95% is excreted in the first 24 hours. Excretion of drug in urine is negligible after 48 hours in healthy adult volunteers (Thorsteinsson and Bergan, 1992). In the same study which had a crossover design, blood taken 1 week or more after a dose always had an undetectable fosfomycin concentration, indicating that 1 week after a dose as high as 4g oral fosfomycin trometamol or 3g fosfomycin sodium, renal clearance of drug is complete.

Food does not decrease total urinary excretion of fosfomycin, it simply delays drug absorption but total amount of drug excreted in the urine over time is the same. Significantly higher urinary concentrations of fosfomycin are achieved after oral administration under fasting conditions as compared to oral administration under fed conditions for the first 4 hours after dose. After 4 hours, however, urinary concentrations of fosfomycin are similar following either oral administration under fasting conditions or oral administration under fed conditions (Kisicki 1994). Mean urinary fosfomycin concentrations after a single 3g oral dose peak at 400-700 ug/ml typically 2-6 hours after the dose, depending on whether food has been given or not. This is typically 100-fold the peak serum concentration when serum is collected at the same time, suggesting that the drug concentrates to a large extent in urine. This means that mean fosfomycin concentrations in urine are maintained above an MIC threshold of 128 ug/mL for at least 24 hours post-dose following either oral administration under fasting conditions or oral administration under fed conditions indicating that the drug can be administered without regard to meals (Kisicki 1994). It also means that the drug is a good candidate for treatment of UTIs due to its marked urinary concentration.

Faecal excretion

In six adult volunteers, the fecal excretion of fosfomycin was evaluated after 3 g fosfomycin administered both orally. The mean fecal recovery at day 4 after the dose was 28.0 ± 11.8 % (Thorsteinsson and Bergan, 1992). In the study by Kisicki (1994), total faecal excretion of drug

was not affected by dosing with or without food. Faecal excretion of the drug over a 5.5 day period was relatively linear by 24-hour period commencing 24 hours after the dose.

Biliary excretion

The possibility of biliary excretion of fosfomycin with enterohepatic circulation has been investigated in 2 volunteers undergoing cholecystectomy (Segre et al. 1987). In two volunteers undergoing cholecystectomy, biliary concentrations varying between 25% and 118% of serum concentrations were found 2-12 hours after unknown oral or IV dosage of fosfomycin. In the same study the appearance of a second serum peak was found, leading the authors to suggesting that fosfomycin is subject to enterohepatic circulation.

The paper by Segre et al (1987) refers to other studies of fosfomycin in bile but these studies are not contained in the dossier. Could the sponsor provide these for evaluation please?

Comment: There are no studies presented in the dossier of biliary concentrations of fosfomycin in normal volunteers ie subjects without biliary inflammation. Could the sponsor provide this study or these studies please? As the total excretion of fosfomycin in a 5.5 day period in 6 volunteers after recovery of drug in urine and faeces is a mean of 71.4% with a standard deviation of 15.2% Kisicki (1994), it is considered that excretion of drug into body fluids other than urine and faeces is not likely to be in clinically significant amounts.

3.2.1.6. Mass balance studies

No studies presented.

3.2.1.7. Intra subject individual variability of PK

No studies were presented in the dossier in which the same subject received the same dose of fosfomycin in the same fasting or fed state on more than one occasion. Hence it is hard to assess intra subject individual variability of PK, i.e. PK of the same subject after repeated single doses interspersed by washout periods of at least one week.

3.2.1.8. Inter subject individual variability of PK

In the study by Thorsteinsson in 12 healthy volunteers, after a 3g oral dose of fosfomycin, bioavailability of the drug was a mean of 32.88% with a standard deviation of 2.3%. Mean plasma AUC was 139.08 ug.h/ml with a standard deviation of 11.376 ug.h/ml and urinary recovery of drug was 39.109% with a standard deviation of 1.93%. Hence, at least in healthy volunteers, the inter subject variability in PK does not appear significant. Likewise, there were no significant differences in the PK between male and female healthy volunteers.

3.2.2. Pharmacokinetics in the target population

The target population for the first proposed indication is adult females aged 12 years or older with acute uncomplicated UTIs. The target population for the 2nd proposed indication is adult males and females undergoing surgical and diagnostic procedures involving the lower urinary tract. No studies presented in the dossier of the PK of adult females with UTI or adults undergoing prophylaxis.

Comment: The PK of fosfomycin in adult females with acute uncomplicated UTI is not likely to be significantly different from the PK in healthy volunteers (noting no significant differences were noted between males and females in healthy volunteers). The patient population is likely to be either sexually active healthy young adult females or older females with UTI. Target population in the prophylaxis indication is adult males and females though age group could be somewhat older and renal function somewhat more impaired than healthy volunteers (due to older age +/- urinary tract disease).

3.2.3. Pharmacokinetics in special populations

3.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

No studies provided in the dossier.

Comment: Recommend add the following to the Product Information: "The pharmacokinetic features of fosfomycin have not been studied in patients with impaired hepatic function. However, fosfomycin does not undergo hepatic metabolism and clearance is known to be predominantly renal with urinary excretion".

3.2.3.2. Pharmacokinetics in subjects with impaired renal function

One study contained in the dossier examines PK in subjects with impaired renal function. In the study by Fillastre (1988) five young healthy adult male volunteers (age 29 +/- 3 years SD) and 23 patients with chronic renal impairment (CRF) had assessment and comparison of the PK of fosfomycin. Patients with CRF were grouped by glomerular filtration rate. Groups were Group 1 - mild renal impairment (creatine clearance 30-50 mls/min), Group 2 - moderate renal impairment (creatine clearance 10-30 mls/min), Group 3 - severe renal impairment (creatine clearance <10 mls/min), and Group 4 - haemodialysis patients. All subjects received a single dose of 25 mg/kg body weight (typically 2g) tromethamine fosfomycin. As renal function decreased (creatinine clearances varying from 54 mL/min to 7 mL/min), the t1/2 of fosfomycin increased from 11 hours to 50 hours. The percent of fosfomycin recovered in urine decreased from 32% to 11% indicating that renal impairment significantly decreases the excretion of fosfomycin. There were linear relationships between fosfomycin PK and glomerular filtration rate data:

$t_{1/2}$ (h) = 0.06 serum creatinine (umol/l) + 0.04 (n=23, r = 0.95, p<0.001);

ke (h^{-1}) = 0.001 C_{cr} (ml/min) + 0.02 (n = 23, r=0.72, p<0.01);

Cr (ml/min) = 1.39 C_{cr} (ml/min) - 13.3 (n=23, r=0.94, p<0.001).

In 5 anuric haemodialysis patients, serum concentrations decreased slowly. T1/2 of fosfomycin during hemodialysis was 40 hours. Serum fosfomycin was still detectable in haemodialysis patients after 2 successive haeodialysis sessions 48-72 hours apart.

Comment: Fosfomycin clearly accumulates if renal function is impaired. The clinical significance of this is unknown. The proposed Australian PI contains the following statements regarding use in patients with renal impairment:

"Special Populations

The pharmacokinetic features of fosfomycin are not modified by age or pregnancy. The drug accumulates in patients with renal failure; linear relationships have been established between fosfomycin pharmacokinetic parameters and glomerular filtration rate data."

And

"Precautions: Renal Insufficiency

Urinary concentrations of fosfomycin remain effective for 48 hours after a usual dose if creatinine clearance is above 10 mL/min."

In contrast the current PI in the USA is much more specific:

"Renal Insufficiency: In 5 anuric patients undergoing hemodialysis, the t1/2 of fosfomycin during hemodialysis was 40 hours. In patients with varying degrees of renal impairment (creatinine clearances varying from 54 mL/min to 7 mL/min), the t1/2 of fosfomycin increased from 11 hours to 50 hours. The percent of fosfomycin

recovered in urine decreased from 32% to 11% indicating that renal impairment significantly decreases the excretion of fosfomycin."

Recommend:

- § Specifying renal impairment or insufficiency as a specific special population
- § Providing more detail in the PI regarding limited data for PK in patients with severe renal impairment or haemodialysis (only 5 patients studied per group), perhaps with a very specific statement akin to the US PI for hemodialysis patients
- § Statement that PK has not been studied in peritoneal dialysis or haemofiltration patients.
- § A stronger statement that the drug accumulates in patients with significant renal impairment

3.2.3.3. Pharmacokinetics in pregnancy

The dossier contains one study by De Cecco (1987) investigating the PK of fosfomycin trometamol in pregnancy. In this Phase 1 study, 4 pregnant females received 50 mg/kg oral fosfomycin trometamol at 27-32 weeks gestation and one month after delivery. It is unclear from the publication whether the subjects had UTI, asymptomatic bacteriuria or were healthy volunteers. Serum and urine samples were collected immediately pre-dose and up to 24 hours after dosing. In this small sample, there were no apparent differences int he 24-hour period after dosing in serum and urinary concentrations during pregnancy compared to post-delivery.

The study by Ferreres (1977) in 10 pregnant women shows that fosfomycin has placental transfer and fetal serum levels reach a mean of 68% of maternal serum levels within 120-210 minutes.

Comment: Pregnancy does not appear to alter the PK of fosfomycin in a small sample of 4 patients. The current Australian PI contains the following statement: "The pharmacokinetic features of fosfomycin are not modified by age or pregnancy". Consider changing this to: "The pharmacokinetic features of fosfomycin do not appear to be modified by pregnancy in a study of 4 pregnant patients."

3.2.3.4. Elderly

Three studies in the dossier examined the PK of fosfomycin trometamol in the elderly. In the study by Fillastre, Leroy, Humbert, Borsa and Josse (1988), five young adult volunteers (age 29.9 +/- 2.7 years SD) and 8 healthy elderly adult volunteers (age 71.8 +/- 6 years SD) received a single dose of 25 mg/kg body weight (typically 2g) tromethamine fosfomycin. Peak serum concentrations and apparent volumes of distribution were not significantly different in the elderly. The mean elimination half-life in young adults was 5.37 +/- 2.56 SD hours and was 8.3 +/- 5.5 SD hours in the elderly with larger individual variability in the elderly. Urinary excretion of fosfomycin by 24 hours was reduced in the elderly with 27.5% +/- 10.6% SD compared to 57.7% +/- 30.2 SD in the young adults. Creatinine clearance was much lower in the elderly with a mean of 48. 8 +/- 17.0 SD mls/min compared to young adults at 179.6 +/- 25.1 SD mls/min. The same study contained a group of 7 patients with mild renal impairment (creatinine clearance 54.2 +/- 24.2 SD mls/min), these patients were aged a mean of 43.7 +/- 22.9 SD years and received the same dose of fosfomycin as the healthy elderly volunteers. PK of these mildly renally impaired patients is similar to the healthy elderly volunteers. Creatinine clearance in both groups was comparable with 54.2 +/- 24.2 SD mls/min in the mildly renally impaired patients compared to 48. 8 +/- 17.0 SD mls/min in the elderly volunteers. This paper suggests that in a small number of patients (8 healthy elderly, 7 mostly younger with mild renal impairment) that PK of fosfomycin is altered by the worsening renal impairment that occurs as a person ages rather than from being elderly per se. The authors recommended no dosage

reduction in elderly patients if creatinine clearance was > 50 mls/min. The same data was included in the paper by Borsa, Leroy, Fillastre et al (1988).

Salvioli (1985) studied 6 elderly fasting hospitalised patients aged 68-88 years given a single 3g oral fosfomycin trometamol dose. Patients with renal impairment were excluded. Creatinine clearance was 94.33 +/- 8.64 SD mls/min which is at the high end of the normal range for all adults but as expected for a group of elderly patients. Cmax was 33.07 +/- 10.12 SD ug/ml which is moderately higher than the 20.9 - 32.0 ug/ml seen in fasting healthy young adult volunteers. Absorption of drug was slower with Tmax at 3 +/- 0.63 hours compared to 2.0-2.3 hours seen in young adults. Urinary recovery was 18.5-61% at 24 hours which is less than in young adults.

In the study by Janknegt (1994), 7 elderly female volunteers aged 71-90 years with impaired renal function (range 21-72 mls/min) living in a nursing home were dosed with a 3g Monuril sachet. Urinary concentrations were measured over an 84-hour period. Elimination half-lives ranged from 7-25 hours with longer half lives correlated with more impaired renal function.

Comment: Elderly patients with good renal function appear to have similar PK to younger adults. Fosfomycin PK is altered by renal impairment rather than age. Elderly patients are more likely to have age-related renal impairment. Currently the proposed Australian PI states "The pharmacokinetic features of fosfomycin are not modified by age". This comment is appropriate.

3.2.3.5. Children

The sponsor has not requested a paediatric indication, although teenage patients 12 years or greater are included in the proposed patient group. The study by Careddu (1987) contains paediatric PK data for 43 children aged 1 month to 15 years (mean 5.7 years) on treatment with fosfomycin tromethamine for UTIs. Three single dose regimens were given (see synopsis 19.1.1.7). In 6 children given a dose of 63.9 +/- 11.6 mg/kg (the closest to the usual adult dose of 3g, assuming a typical adult weight of 70 kg), PK parameters were very similar to adults. Urinary recovery at 24-48 hours was 27.6-50.1% at the 63.9 +/- 11.6 mg/kg dose. This is similar to adults.

Comment: The proposed Australian PI states "The pharmacokinetic features of fosfomycin are not modified by age". This comment is appropriate.

3.2.3.6. Pharmacokinetics related to genetic factors

No studies provided

3.2.3.7. Lactation

No data presented.

Comment: The proposed Australian PI states "Use in lactation. Fosfomycin is excreted in breast milk. Monurol therapy should therefore not be used in breastfeeding mothers unless the potential benefit outweighs the potential risks."

The PI from the United States (dated 2011) states "Nursing Mothers. It is not known whether fosfomycin tromethamine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Monurol, a decision should be made whether to discontinue nursing or to not administer the drug, taking into account the importance of the drug to the mother."

The dossier does not appear to contain any information about the excretion of fosfomycin into breast milk. Could the Sponsor please provide further information and / or human studies as to whether fosfomycin is excreted into breast milk? Is the comment based on studies in animals?

3.2.4. Pharmacokinetic interactions

3.2.4.1. Cimetidine

In the study by Bergan et al (1988), 9 fasting healthy young adult male volunteers, 400 mg oral cimetidine given the night prior and also 30 minutes before a fosfomycin trometamol dose of 50 mg/kg body weight did not alter the PK of fosfomycin.

3.2.4.2. Metoclopramide

In the study by Bergan et al (1988), the same 9 fasting healthy young adult male volunteers were given 20 mg oral metoclopramide 30 minutes before a fosfomycin trometamol dose of 50 mg/kg body weight. Compared to the same volunteers given fosfomycin alone (note a washout period between the two arms of the study), the rate of absorption of fosfomycin was slowed, serum concentrations were lowered, half-life was prolonged, and AUC was reduced. The postulated mechanism is that metoclopramide increased gastric and intestinal motility with quicker passage through the area of the gut with maximum fosfomycin absorption. As a result, fosfomycin is absorbed at lower levels of the gut over a longer period of time. Mean total urinary recovery of fosfomycin reduced over a 48 hour period reduced form 36.1 +/- 6% for fosfomycin alone compared to 27.7 +/- 5.1% for metoclopramide with fosfomycin. No urinary elimination data was presented beyond 48 hours.

No data was presented in the dossier, but other drugs which increase gastrointestinal motility could have the same interaction with fosfomycin as metoclopramide. A sentence to this effect has been included in the proposed PI.

Comment: Metoclopramide interacts with fosfomycin in a small study of healthy young adult males, the likely mechanism is increased gastrointestinal motility. In the proposed PI, the following comment is included: "Concomitant administration of metoclopramide has been shown to lower serum and urinary concentrations of fosfomycin and should be avoided. Other drugs that increase gastrointestinal motility may produce similar effects. Interaction studies have only been performed in adults."

This comment is satisfactory.

3.2.4.3. Lithium

Some publications in the dossier refer to an interaction of fosfomycin with lithium, but no further information is provided.

Comment: Could the Sponsor provide further information as to whether lithium interacts with fosfomycin? If there is an interaction, the draft Product Information will need to be modified.

3.2.4.4. Balsalazide

Some publications in the dossier refer to an interaction of fosfomcyin with balsalazide, but no further information is provided. For example, this is discussed in the review paper by Michalopoulos (2011) contained in the dossier.

Comment: Could the Sponsor provide further information as to whether balsalazide interacts with fosfomycin? If there is an interaction, the draft Product Information will need to be modified.

3.3. Evaluator's overall conclusions on pharmacokinetics

3.3.1. Summary of pharmacokinetics

3.3.1.1. Sachet composition

- A sachet of Monurol contains 5.631g fosfomycin trometamol (equivalent to 3.0 g active fosfomycin), mandarin and orange juice flavour, saccharin and sucrose.

3.3.1.2. Absorption

- A single Monurol granules for oral solution sachet is dissolved into a glass of water and taken immediately after preparation. Fosfomycin trometamol salt is rapidly absorbed in the gut and converted to the active drug fosfomycin.
- The mean absolute bioavailability of fosfomycin trometamol in three studies of fasting healthy adult volunteers was 33 - 46%.
- Fosfomycin trometamol is substantially more orally bioavailable than calcium fosfomycin based on comparative early studies.
- The proposed formulation is the same as that used in the majority of PK, efficacy and safety studies with only the orange flavour agent changed.
- The proposed formulation with the current orange flavouring agent has been commercially available in Europe since the 1980s and is the same formulation currently used in Australia under the SAS scheme.
- Only a single dosage form and strength is proposed.
- In fasting healthy adult volunteers, mean Cmax of 20.9–32.0 μg/mL was reached within about 2 h following administration of a single sachet of Monurol (active drug 3g fosfomycin).
- AUC24 for this dose is 120-184 ug.h/ml in fasting healthy adult volunteers.
- High fat food reduced the bioavailability of fosfomycin trometamol in healthy adult volunteers from 37% to 30% and decreased the rate and extent of absorption. It lowered Cmax by approximately 25% and delayed peak drug levels by a further 2 h with Tmax at 4.0 h. It lowered AUC_{24} from 184 ug.h/ml to 154 ug.h/ml.

3.3.1.3. Distribution

- The apparent volume of distribution of fosfomycin in healthy volunteers was 16-21 litres, approximately the size of the extracellular fluid compartment indicating that the drug distributes widely into extra-vascular compartment.
- Plasma protein binding was 0% in a study of 10 healthy adult volunteers. No other data is available on plasma protein binding.
- Fosfomycin penetrates the prostate well achieving 57-100% serum levels (mean 90%) in 6 males undergoing prostectomy for adenomas.
- Fosfomycin achieves high levels in bladder tissue.
- Fosfomycin is transferred via the placenta in pregnancy with fetal serum levels a mean of 68% 2-3.5 h after maternal intramuscular dosage of sodium fosfomycin. There are no studies of placental transfer of the oral formulations but as the parenteral and oral formulations convert to fosfomycin active drug, presumably the oral formulation also has high placental transfer although the PK of this is unknown.

3.3.1.4. Metabolism

- Fosfomycin does not undergo metabolism and is primarily excreted unchanged in the urine.

3.3.1.5. Renal clearance and urinary excretion

- Total body clearance and renal clearance are similar so non-renal clearance is thought to be negligible.
- Total clearance of fosfomycin corresponds closely to the glomerular filtration rate, so neither tubular secretion nor reabsorption are thought to occur.
- In healthy adult volunteers, up to 40% of an orally administered dose of fosfomycin tromethamine equivalent to 3g fosfomycin is excreted in the urine within 48 h and, of this, approximately 85 to 95% is excreted in the first 24 h.
- Excretion of drug into urine is minimal after 48 h in healthy adult volunteers and in this group when tested 7 days after dosing, serum levels were undetectable.
- Food delays drug absorption but the total amount of drug excreted in the urine over time is the same. This means that the drug can be administered without regard to meals.
- For the first 4 h after a dose, higher urinary concentrations of fosfomycin are noted in fasting states compared to fed states. After 4 h, urinary concentrations are similar in either fasting or fed states.
- Mean urinary fosfomycin concentrations after a single 3g oral dose peak at 400-700 ug/ml 2 h (fasting) to 6 h (fed state) after the dose.
- Fosfomycin concentrates in urine, with mean peak urinary concentrations typically 100 times more than the mean peak serum concentrations.
- Mean urinary fosfomycin concentrations are maintained above an MIC threshold of 128 ug/mL for at least 24 h post 3g oral dose in either the fasting or fed state.
- Fosfomycin is a good candidate for treatment of UTIs due to its marked urinary concentration.

3.3.1.6. Other forms of excretion

- Mean faecal recovery at day 4 after the 3g oral fosfomycin dose was 28.0 ± 11.8 % in 6 healthy adult volunteers.
- Total faecal excretion of drug was not affected by dosing with or without food.
- Faecal excretion of the drug over a 5.5 day period was relatively linear by 24-h period commencing 24 h after the dose.
- Data on biliary excretion of fosfomycin provided in the dossier is limited. The presence of two serum peaks in one PK study suggests that fosfomycin could undergo enterohepatic circulation.
- In two volunteers undergoing cholecystectomy, biliary concentrations varying between 25% and 118% of serum concentrations were found 2-12 h after unknown oral or IV dosage of fosfomycin.
- Further information on biliary concentrations of fosfomycin in subjects without biliary inflammation has been requested from the Sponsor.

3.3.1.7. Intra and inter individual variability of PK

- No data is available on intra-subject variability of PK.
- In healthy adult volunteers after a 3g oral dose, bioavailability of the drug in one study was a mean of 32.88% with a standard deviation of 2.3%. Mean plasma AUC was 139.08 ug.h/ml with a standard deviation of 11.376 ug.h/ml and urinary recovery of drug was 39.109%

with a standard deviation of 1.93%. Hence, at least in healthy volunteers, the inter subject variability in PK does not appear significant.

- There are no significant differences in the PK between male and female healthy adult volunteers.

3.3.1.8. Pharmacokinetics in the target population

- Target population for the first proposed indication (treatment) is females with acute uncomplicated symptomatic UTI aged 12 years and older. No PK data has been presented in this target population but younger adult females are likely to have similar PK to healthy adult female volunteers. PK data has been presented in elderly females without UTI and in patients with renal impairment without UTI, see below.
- Target population for the second proposed indication (prophylaxis) adult males and females requiring prophylaxis. PK data has not been presented for this target population but has been presented in the elderly and in patients with renal impairment, see below.

3.3.1.9. Pharmacokinetics in subjects with impaired hepatic function

- No data.

3.3.1.10. Pharmacokinetics in subjects with impaired renal function

- Fosfomycin primarily undergoes renal excretion with a linear relationship between pharmacokinetics and glomerular filtration rate.
- Fosfomycin PK has been studied after 25 mg/kg oral dosage fosfomycin trometamol in 23 subjects with mild, moderate or severe renal impairment. As renal function decreased (creatinine clearances varying from 54 mL/min to 7 mL/min), the t1/2 of fosfomycin increased from 11 h to 50 h. The percent of fosfomycin recovered in urine decreased from 32% to 11% indicating that renal impairment significantly decreases the excretion of fosfomycin.
- The linear relationship between fosfomycin PK and glomerular filtration rate data has been mathematically described:

  $t_{1/2}$ (h) = 0.06 serum creatinine (umol/l) + 0.04 (n=23, r = 0.95, p<0.001);
  ke (h^{-1}) = 0.001 C_{cr} (ml/min) + 0.02 (n = 23, r=0.72, p<0.01);
  Cr (ml/min) = 1.39 C_{cr} (ml/min) - 13.3 (n=23, r=0.94, p<0.001).

- In 5 anuric haemodialysis patients, serum concentrations decreased slowly. T1/2 of fosfomycin during hemodialysis was 40 h. Serum fosfomycin was still detectable in haemodialysis patients after 2 successive haeodialysis sessions 48-72 h apart.
- Fosfomycin accumulates if renal function is impaired. The clinical significance of this accumulation is unknown.

3.3.1.11. Pharmacokinetics in pregnancy

- In a study of 4 pregnant females who received 50 mg/kg oral fosfomycin trometamol at 27-32 weeks gestation and one month after delivery, there were no apparent differences in the 24-h period after dosing in serum and urinary concentrations during pregnancy compared to post-delivery. Thus, it is not likely based on one small study that pregnancy significantly alters the PK of fosfomycin.
- Fosfomycin transfers across the placenta to a large extent.

3.3.1.12. Pharmacokinetics in the elderly

- In a study of 6 elderly fasting hospitalised patients aged 68-88 years, a single 3g oral fosfomycin trometamol dose was given. Patients with renal impairment were excluded.

Mean creatinine clearance was 94.33 mls/min which is at the high end of the normal range for all adults but as expected for a group of elderly patients. Mean Cmax was 33.07, slightly higher than that seen in other studies in healthy young adults. Absorption of drug was slower than in young adults with mean Tmax at 3 h. Urinary recovery was 18.5-61% at 24 h, again less than in young adults.

- In a study of 7 elderly female volunteers living in a nursing home aged 71-90 years with impaired renal function (range 21-72 mls/min) a 3g Monuril sachet was given. Urinary concentrations were measured over an 84-h period. Elimination half-lives ranged from 7-25 h with longer half lives correlated with more impaired renal function.
- The PK of fosfomycin has been studied in 8 healthy elderly adult volunteers and compared to 5 young healthy adult volunteers. All received a single dose of 25 mg/kg body weight tromethamine fosfomycin. Peak serum concentrations and apparent volumes of distribution were not significantly altered by age. The mean elimination half-life in young adults was 5.37 h and 8.3 h in the elderly. Mean urinary excretion of fosfomycin by 24 h was reduced in the elderly at 27.5% compared to 57.7% in the young adults. Mean creatinine clearance was much lower in the elderly at 48. 8 mls/min compared to young adults at 179.6 mls/min.
- The same study examined the same dose of fosfomycin in 7 patients with mild renal impairment (creatinine clearance 54.2 +/- 24.2 SD mls/min) aged a mean of 43.7 +/- 22.9 SD years. PK of fosfomycin in these mildly renally impaired patients was similar to the healthy elderly volunteers. Creatinine clearance in both groups was comparable in both groups. Hence, PK of fosfomycin is altered by the worsening of renal impairment that occurs naturally as a person ages.
- In summary, the PK of fosfomycin is likely dependent on renal function and independent of age itself.

3.3.1.13. Pharmacokinetics in children and teenagers

- The sponsor has not requested a paediatric indication, although teenage patients 12 years or greater are included in the proposed patient group.
- One study contains paediatric PK data for 43 children aged 1 month to 15 years (mean 5.7 years) on treatment with oral fosfomycin tromethamine for UTIs. In 6 children given a mean dose of 63.9 mg/kg (the closest to the usual adult dose of 3g, assuming a typical adult weight of 70 kg), PK parameters were very similar to adults in other studies. Urinary recovery at 24-48 h was 27.6-50.1%, similar to the range in other studies of adults.
- PK data is very limited in children and young adults, but in teenagers aged 12 or older, based on the limited data, PK at the same dose by body weight is likely similar to that seen in adults.

3.3.1.14. Pharmacokinetics related to genetic factors

- No studies provided.

3.3.1.15. Pharmacokinetics in lactation

- No data presented.

3.3.1.16. Pharmacokinetics in other special populations, with other population characteristics *or in other acute or chronic disorders*

- No data presented.

3.3.1.17. Pharmacokinetics and ethnicity

- No data presented.

3.3.1.18. Population pharmacokinetics

- No studies provided.

3.3.1.19. Effect of cimetidine on pharmacokinetics of fosfomycin

- No interaction noted in a study of 9 healthy adult volunteers.

3.3.1.20. Effect of metoclopramide on pharmacokinetics of fosfomycin

- In a study of 9 fasting healthy young adult male volunteers given 20 mg oral metoclopramide 30 minutes before a fosfomycin trometamol dose of 50 mg/kg, the rate of absorption of fosfomycin was slowed, serum concentrations were lowered, half-life was prolonged, and AUC was reduced.
- In the same study, urinary excretion of fosfomycin over a 48-h period was reduced if metoclopramide was given. Total urinary recovery of fosfomycin over a 48 h period was 36.1% for fosfomycin alone compared to 27.7% for metoclopramide with fosfomycin.
- The postulated mechanism is that metoclopramide increased gastric and intestinal motility with quicker passage through the area of the gut with maximum fosfomycin absorption. As a result, fosfomycin is absorbed at lower levels of the gut over a longer period of time.

3.3.1.21. Other possible pharmacokinetic interactions

- No data was presented, but other drugs which increase gastrointestinal motility could have a similar interaction with fosfomycin as does metoclopramide.
- Fosfomycin does not undergo metabolism within the body, so there are not likely to be any hepatic cytochrome P450 interactions with other drugs, although this has not been studied.
- Fosfomycin is not bound to plasma proteins, so there are not likely to be drug interactions with plasma protein-bound drugs, although this has not been studied.
- Apart from metoclopramide and cimetidine, no other data or studies on potential pharmacokinetic interactions with other drugs was presented in the dossier.

3.3.2. Limitations of PK studies

- Fosfomycin is the first and only drug in its class, so PK results cannot be extrapolated from any other drug.
- PK studies in the dossier are uniformly old, with all PK studies in the dossier published between 1977 and 1994. This means that our current knowledge of the PK of fosfomycin is based on data that is more than 20 years old, with all the limitations of the PK studies conducted mostly in the 1980s and early 1990s.
- There is no new PK data that the evaluator is aware of for single 3g oral fosfomycin that has been published in the last 20 years.
- Despite these limitations, the PK of single 3g oral fosfomycin dose has been sufficiently well-studied in healthy adult volunteers and results across studies were reasonably consistent.
- The PK of single 3g oral fosfomycin has not been studied in the target treatment population, but the PK of young adult females with acute uncomplicated UTIs can be extrapolated from the PK studies in healthy adult volunteers.
- The PK of single 3g oral fosfomycin has not been studied in older adult females with acute uncomplicated UTI, but data can be extrapolated from the three PK studies conducted in the elderly and the one PK study conducted in renally impaired subjects.

- Only one PK study has been conducted in patients with renal impairment or haemodialysis. This study was well-conducted but in small numbers of subjects. This study is quite old having been published in 1988.
- No data is available in patients undergoing peritoneal dialysis or haemofiltration methods.
- No data is available in patients with hepatic impairment but the drug does not undergo hepatic metabolism.
- The PK of fosfomycin in patients with other acute or chronic disorders is unknown.
- The data for PK in pregnancy is limited and is based on a single study published in 1987 of 4 pregnant patients only.
- The sponsor states in the proposed PI that fosfomycin is distributed into breast milk but the dossier does not appear to contain any human or animal data or studies to support this statement.
- The sponsor has requested a treatment indication for females aged 12 years or older. There is only one PK study in the dossier for children and teenagers. PK data in teenagers is limited but PK parameters at the same dosage by body weight as adults appear similar to adults.
- The PK related to ethnicity is unknown.
- The PK of multiple doses of fosfomycin has not been well-studied, and all PK studies in the dossier were for single dose fosfomycin only. The optimum dosage interval between a first, second and third dosage of fosfomycin is unknown, should more than one dose be required. The sponsor has requested a 3g single dose for the treatment of uncomplicated UTI (indication 1), and there is sufficient PK data in the dossier to support this dose. However, the sponsor has requested a surgical prophylaxis indication of a 3g dose 3 h prior to surgery followed by a 2nd dose 24 h after surgery but has not provided any PK data for this dosage regimen.
- The plasma protein binding data is limited. It is based on a single study of 10 volunteers published in 1969.
- The proposed PI states that fosfomycin is distributed into the seminal vesicles, but this data has not been provided.
- Data on possible enterohepatic circulation of the drug is largely based on the presence of 2 peaks in serum with some supporting data missing from the dossier.
- Data on biliary excretion is largely based on biliary levels in 2 volunteers undergoing cholecystectomy with some supporting data missing from the dossier.
- Studies of possible PK drug interactions are limited to metoclopramide and cimetidine only.

3.3.2.1. Questions regarding the PK studies

- Could the sponsor please provide further animal or human data regarding the distribution of fosfomycin into breast milk? Note the differences between the proposed Australian data which states that the drug is distributed into breastmilk and the PI in the USA stating that it is unknown whether the drug is excreted into breastmilk.
- Could the sponsor please provide the full poster or publication by Chezzi (1989) regarding the penetration of fosfomycin into seminal vesilces? The abstract in the dossier does not contain sufficient information.
- Is the sponsor aware of any PK data in peritoneal dialysis or haemofiltration?

- Could the sponsor provide more data regarding the biliary excretion and enterohepatic circulation of drug, specifically the publications referred to in the paper by Segre (1987) contained in the dossier?
- Is the sponsor aware of any other studies regarding PK drug interactions? Why do some of the early publications refer to possible fosfomycin interactions for lithium or balsalazide? Could the sponsor provide these studies? If not, could the sponsor comment on whether there is a potential interaction?

Fosfomycin accumulates in patients with renal impairment however the clinical significance of this appears to be unknown. The last sentence in the publication by Fillastre (1988) recommends dosage reduction in patients with chronic renal sufficiency however this has not been recommended in the proposed PI. Could the Sponsor comment further? Is the sponsor aware of any data regarding the accumulation of the drug in patients with renal failure and any negative potential consequences of this?

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic information

Pharmacodynamic studies of fosfomycin are mostly included in the nonclinical study reports, which have been evaluated by the nonclinical evaluator. However, there are some important clinical pharmacodynamic issues and issues of microbiology and resistance development which require discussion and review in the clinical evaluation of fosfomycin.

The pre-clinical and clinical development of fosfomycin in the late 1970s and early 1980s predates the development of antimicrobial pharmacodynamics. At that time, it was not a regulatory requirement to have a detail assessment of the pharmacodynamics of a any new candidate antimicrobial agents. Hence, the pharmacodynamics studies of fosfomycin are extremely limited.

Below shows the studies related to each pharmacodynamic topic.

Table 3: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	In vitro pharmacodynamics	Mazzei 2006[18]	*
		Wiedemann 1987[19]	*
		Greenwood 1987[20]	*
	Bacteriostatic effect	Bergan 1990[21]	*
	In vivo pharmacodynamics	Carlone 1987[22]	*
	Bacterial resistance	Gupta 2005[23]	*

[18] Study objectives: To investigate the in vitro pharmacodynamics including postantibiotic effect (PAE) of fosfomycin.
[19] Study objectives: To assess the pharmacodynamics particularly bacterial kill in an in vitro model.
[20] Study objectives: To test the activity of fosfomycin against E. coli in an in vitro dynamic bladder model.
[21] Study objectives: To study the antibacterial effect of fosfomycin in urine.
[22] Study objectives: To assess the adhesive properties of fosfomycin on bacteria isolated from the urine of patients with UTIs, and to compare these properties to those of norfloxacin and cotrimoxazole.

PD Topic	Subtopic	Study ID	*
	development	Wiedemann 1987[24] Greenwood 1987[25]	
Secondary Pharmacology	Secondary pharmacodynamic effects	No studies	
Gender other genetic and Age Related Differences in PD Response	Effect of gender	No studies	
	Effect of genetic characteristic	No studies	
	Effect of age	No studies	
PD Interactions	Any drug	No studies	
Population PD and PK-PD analyses	Healthy subjects	No studies	
	Target population	No studies	

* Indicates the primary PD aim of the study.

No PD studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacodynamics

4.2.1. Mechanism of action

Fosfomycin is a phosphonic acid antibiotic of natural origin isolated for the first time from a culture of Streptomyces fradiae in Spain in 1969 (Stapley et al., 1970). Fosfomycin's mechanism of action is the interference with bacterial cell wall synthesis. Kahan et al (1974) identified the specific cell wall enzyme inhibited by fosfomycin as the phosphoenolpyruvate UDP-GlcNac-3-enolpyruvyl transferase, which is responsible for the first step in the synthesis of bacterial cell walls.

Fosfomycin's mechanism of action is unique. Its action at the first stage of peptidoglycan synthesis in the bacterial cell wall is a different stage of cell wall synthesis than the beta-lactam antibiotics such as penicillins and cephalosporins. For this reason and also because fosfomycin is the only antibacterial agent in its class, cross-resistance with other antibiotics is unlikely.

Before fosfomycin can exert its effect on cell wall synthesis, fosfomycin must first gain entry to the bacterial cell and this is achieved by making use of the L-alpha-glycerophosphate transport system or alternatively the hexose phosphate pathway (Greenwood, 1987). Uptake via the L-alpha-glycerophosphate transport system is inhibited by phosphate ions, so that media containing phosphate buffers are unsuitable for testing fosfomycin activity. The alternative hexose phosphate pathway operates only under conditions of induction by hexose phosphates, and this is the basis of the potentiation of the activity of fosfomycin by glucose-6-phosphate (Greenwood, 1987). In vivo, fosfomycin was 2-8x less active by MIC testing in pooled human

[23] Study objectives: To assess the relative effects of fosfomycin, ciprofloxacin and nitrofurantoin on E. coli isolated from bowel flora in women after treatment for uncomplicated UTI.
[24] Study objectives: To assess the pharmacodynamics particularly bacterial kill in an in vitro model.
[25] Study objectives: To test the activity of fosfomycin against E. coli in an in vitro dynamic bladder model.

urine against 8 strains of E coli if there was no supplemental glucose-6-phosphate added to the urine (Greenwood, 1987).

4.2.2. Fosfomycin antimicrobial susceptibility testing

Fosfomycin trometamol is not calibrated for antimicrobial susceptibility testing against many bacteria, according to current clinical microbiology guidelines. This is an important consideration in the regulatory process and hence will be discussed further in this section. The two major antimicrobial susceptibility testing guidelines used in Australian clinical microbiology laboratories are CLSI and EUCAST guidelines.

4.2.2.1. EUCAST

The document (Fosfomycin trometamol: Rationale for the EUCAST clinical breakpoints v1.0 Feb 2013) is a useful document. This is the current document regarding fosfomycin susceptibility testing using EUCAST methodology. In this document, fosfomycin trometamol breakpoints are only set for the Enterobacteriacae genus (this genus of aerobic gram negative bacteria includes *E coli, Proteus mirabilis, Klebsiella, Serratia* etc). For this genus, fosfomycin EUCAST MIC breakpoints are <32 mcg/ml (susceptible) and >64 mcg/ml (resistant). EUCAST methods that can be used are disc, gradient MIC strip, agar dilution, broth dilution or commercial systems. All methods must have additional glucose-6-phosphate supplementation (see Methods of Action for further information about the reasoning for this). Breakpoints are ONLY set for *Enterobacteriaceae* causing acute uncomplicated UTIs treated with a single oral dose of 3g fosfomycin trometamol. Fosfomycin breakpoints are NOT set for other urinary pathogens such as *Pseudomonas, Staphylococcus saphrophyticus,* or *Enterococcus.* Of note, the EUCAST document states that there are no known Monte Carlo simulations or known PK/PD breakpoints for fosfomycin. It also notes that there is recent development of widely distributed fosfomycin-resistant ESBL-producing *E coli* clones.

4.2.2.2. CLSI

The current CLSI guidelines ((CLSI) Jan 2016) only contain breakpoints and guidelines for *E coli* and *Enterococcus faecalis,* both from urinary tract isolates only. Current MIC breakpoints for both are <64 mcg/ml (susceptible), 128 mcg/ml (intermediate), and >256 mcg/ml (resistant). Disc and agar dilution CLSI methods are approved provided there is supplemental glucose-6-phosphate. Broth dilution fosfomycin susceptibility testing is not approved for fosfomycin. Importantly, NO OTHER bacterial species apart from *E coli* and *Enterococcus faecalis* have susceptibility testing guidelines using CLSI methodology.

4.2.2.3. Summary of antimicrobial susceptibility testing

Fosfomycin susceptibility testing methodology and guidelines are only available for *E coli* (both CLSI and EUCAST methods), other *Enterobacteriaceae* spp (EUCAST) and *Enterococcus faecalis* (CLSI). This means that some common urinary pathogens such as *Staph saphrophyticus* currently have no accredited fosfomycin antimicrobial resistance testing methodology.

4.2.3. Antimicrobial activity of fosfomycin

Many of the studies of fosfomycin susceptibility are old, having been performed when the drug was originally approved in Europe in the 1980s. As the data in these studies is so old, the original data is of little value in an absolute sense, although they are of use when considering fosfomycin resistance development in countries with a long market exposure to the drug.

Current international susceptibility data for Europe and other countries will be discussed. There is also a small amount of local Australian fosfomycin susceptibility testing data, although the drug has had limited availability only on the SAS scheme, so many laboratories do not routinely test for this drug. In my experience, many laboratories only test for fosfomycin for urinary pathogens that are resistant to other oral antibiotics.

The paper by Barry (1995) does require some clinical consideration. It is a paper of antimicrobial susceptibility of urinary isolates from patients in the USA with UTIs. Historically this predates the approval of fosfomycin by the FDA in 1996. Isolates were tested using NCCLS methodology (now named CLSI) by agar dilution with supplemental glucose-6-phosphate. Thus, as fosfomycin is unlikely to have had much use in the USA at that time, it shows natural inate fosfomycin resistance unaffected by any community usage of fosfomycin. It also seeks to highlight non-*E coli* urinary pathogens and their susceptibility patterns. It is difficult to evaluate the bacteriological efficacy of fosfomycin against these less common uropathogens even in the large patient numbers seen in the 3 pivotal efficacy trials discussed earlier, due to the predominance of *E coli* as a uropathogen. It should also be noted that there were then and still are now no susceptibility breakpoints for *Staph, Enterococcus,* and *Pseudomonas* using EUCAST guidelines. There are ONLY E coli breakpoints using CLSI guidelines. However, if one extrapolates the current CLSI susceptibility breakpoint for E coli of <64 mg/L to the other bacterial species, the table below shows there are intrinsic fosfomycin resistance issues in some bacterial species. Specifically, 10-20% of *Enterobacter* species are resistant, 50% of *Morganella morganii* have an MIC of >256 mg/L, 7-16% of *Providencia* spp. are resistant, 50% of *Acinetobacter* spp. have an MIC of >128 mg/L, and 50% of *Staph saphrophyticus* have an MIC of >64 mg/L. Also, *Pseudomonas* and *Enterococcus* spp. are frequently but not uniformly resistant. *Acinetobacter* and *Stenotrophomonas* are usually resistant.

Table 4: Antimicrobial activity of fosfomycin trometamol (from Barry, 1995)

Table. In-vitro activity of fosfomycin trometamol against 3,176 bacterial isolates, expressed as mg/L of fosfomycin tested in the presence of glucose-6-phosphate (25 mg/L)

Species MIC (mg/L) (no. of isolates)	Fosfomycin MIC (mg/L) range	50%	90%	≤64	128	% with ≥256
E. coli (1597)	≤2·0–128	≤2·0	≤2·0	>99	<1	0
Citrobacter diversus (50)	≤2·0–16	≤2·0	4·0	100	0	0
Citrobacter freundii (100)	≤2·0–64	≤2·0	≤2·0	100	0	0
Enterobacter aerogenes (102)	≤2·0–512	16	64	97	1	2
E. agglomerans (48)	≤2·0–>512	16	256	77	10	13
Enterobacter cloacae (102)	≤2·0–>512	16	128	86	12	2
Klebsiella oxytoca (51)	4·0–64	8·0	32	100	0	0
Klebsiella pneumoniae (184)	≤2·0–>512	16	128	89	3	8
Serratia marcescens (98)	≤2·0–64	8·0	32	100	0	0
Proteus mirabilis (102)	≤2·0–>512	≤2·0	32	96	2	2
Proteus vulgaris (49)	≤2·0–256	≤2·0	8·0	96	2	2
M. morganii (49)	8·0–>512	256	512	25	24	51
Providencia rettgeri (41)	≤2·0–512	8·0	64	93	2	5
Providencia stuartii (44)	≤8·0–>512	16	128	84	7	9
Acinetobacter spp. (47)	8·0–512	128	512	32	60	8
Pseudomonas aeruginosa (100)	4·0–>512	32	64	92	5	3
Stenotrophomonas maltophilia (49)	16–512	64	128	63	33	4
S. saprophyticus (128)	≤2·0–>512	64	>512	52	12	36
E. faecalis (196)	16–64	32	64	100	0	0
Enterococcus faecium (33)	16–128	32	64	94	6	0
Enterococcus durans (6)	32–>512	32	>512	67	0	33

What is the most recent antimicrobial susceptibility data available for fosfomycin against common uropathogens? Fosfomycin has been in widespread usage across Europe since approval in many European countries in the 1980s and 1990s. In a fairly recent international surveillance study conducted in 9 European Countries or Brazil called the Antimicrobial Resistance Epidemiological Survey on Cystitis (ARESC) Study (Naber K 2008), urine isolates from female patients aged 18-65 years with uncomplicated lower UTI have been analysed. Patients with recurrent UTIs or pregnancy were included, though patients on prophylactic antibiotics or with structural abnormalities or renal impairment were excluded. Within 3,018 pathogens cultured, E.coli was most frequent uropathogen (76.7%). *E coli* susceptibilities were

as follows: fosfomycin (98.1%), mecillinam (95.8%), nitrofurantoin (95.2%) and ciprofloxacin (91.3 %).

In the paper by Schito (G. L. Schito GC 2010), *E coli* ARESC resistance data is presented as an aggregate for the 10 countries (2315 isolates). The MIC range is 1-512 mg/L, with MIC_{50} of 2 mg/L and MIC_{90} of 8 mg/L, and 0.6% of *E coli* isolates had an MIC of >128 mg/L. The European country with the highest fosfomycin resistance rate for *E coli* was Spain at 1.2% (N. K. Schito GC 2009). In the same study, the most common uropathogens after *E coli* were *Klebsiella pneumoniae, Proteus mirabilis* and *Staphylococcus saphrophyticus,* all of similar incidence at 3.4-3.6%. Fosfomycin resistance rates were 5.6% for *Klebsiella pneumoniae* and 9.7% for *Proteus mirabilis,* using an extrapolated CLSI resistance breakpoint of >256 mg/L, as these organisms are not calibrated for susceptibility testing using CLSI guidelines. Fosfomycin susceptibility could not be reported for *Staph saphrophyticus* as there are no known breakpoints or closely related bacterial species allow possible extrapolation of breakpoints.

Is there any antimicrobial susceptibility data for fosfomycin in the Asia-Pacific region and, if so, how recent is it? There is extremely limited data for Australian isolates, as previously discussed. Fosfomycin trometamol has been commercially available in Taiwan since 2004 (PSUR Jan 2005-2009). The paper by Lu (Lu CL 2011) reports fosfomycin susceptibility for 960 strains of "commonly isolated bacteria associated with UTI" at a single large Taiwanese university hospital from 2007-8. It is assumed although not explicitly specified that these were predominantly urinary isolates. The study employed disc and agar dilution CLSI and EUCAST methods and breakpoints and have extrapolated these methods and breakpoints to closely related species where possible. The results are summarised in tabular fashion below. *E coli* was uniformly susceptible, *Klebsiella pneumoniae* was usually susceptible, *Enterobacter cloacae* was 72-85% susceptible. Other *Enterobacteriaceae* were not tested. The study notes that fosfomycin had no useful activity against *Acinetobacter baumaniae* and susceptibility against *Pseudomonas* was highly variable between the two methods due to the different breakpoint. *Stenotrophomonas* was usually resistant using EUCAST but not CLSI breakpoints. Fosfomycin was very active against MRSA and MSSA and was also active against *E faecalis* regardless of whether strains were VRE or VSE. Activity against *E faecium* was variable depending on which method was used and whether strains were VRE or VSE.

Table 5: Antimicrobial susceptibility of fosfomycin trometamol (from Lu, 2011).

Species	No of strains	% isolates with MIC less than or equal than CLSI breakpoint*	% isolates with MIC less than or equal to EUCAST breakpoint*
E coli	100	100	100
K pneumoniae	100	92	85
Enterobacter cloacae	100	85	72
Acinetobacter baumaniae	100	3	0
Pseudomonas aeruginosa	100	80	29
Stenotrophomonas	100	59	1

Species	No of strains	% isolates with MIC less than or equal than CLSI breakpoint*	% isolates with MIC less than or equal to EUCAST breakpoint*
VRE faecalis	30	100	96.7
VSE faecalis	50	99	94
VRE faecium	30	86.7	26.7
VSE faecium	50	95	62
MRSA	100	89	89
MSSA	100	100	100

* CLSI breakpoints used were <64 mg/L; EUCAST breakpoints used were <32 mg/L. VRE, vancomycin-resistant; VSE, vancomycin-susceptible; MRSA, methicillin-resistant *S aureus;* MSSA, methicillin-susceptible *S aureus.*

EUCAST has published the document "Fosfomycin trometamol: rationale for the EUCAST breakpoints" in 2013 (Testing Feb 2013). It contains a table of MIC distributions from multiple sources and time periods. If a breakpoint of <32 mg/L is used for fosfomycin susceptibility, the following resistance groupings can be made.

Table 6: Common resistance patterns for fosfomycin trometamol

Commonly fosfomycin susceptible species:
Citrobacter spp
Enterococcus faecalis
E coli
Klebsiella spp
Proteus spp
Providencia spp (few strains tested)
Haemophilus influenzae (few strains tested)
Shigella spp (an uncommon uropathogen)
S aureus
S epidermidis (an uncommon uropathogen)
Streptococcus pneumoniae (an uncommon uropathogen)
Species which are frequently resistant:
Enterobacter spp
Pseudomonas aeruginosa
Serratia marcescens
Staph saphrophyticus
Strep pyogenes (an uncommon uropathogen)
Enterococcus faecium
Species which are usually resistant
Acinetobacter spp

In the review of fosfomycin by Keating (2013), susceptibility rates for various uropathogens for the period 2002-2013 were presented. Susceptibility for *E coli* was 97.2-100% (9389 isolates) (including susceptibility of 86-100% against ESBL-producing isolates of E coli), 69.8-84.6% for *Klebsiella pneumoniae* (490 isolates) (including 57.6-100% for ESBL-producing isolates), 80.2-

96.7% for *Proteus mirabilis* (300 isolates) and 20.6-100% for *Staph saphrophyticus* (55 isolates). For other Gram-negative organisms, *Pseudomonas aeruginosa* (40 isolates), *Enterobacter* spp. (16 isolates), and *Acinetobacter baumannii* (11 isolates) had fosfomycin susceptibility rates of 85, 75 and 9 %, respectively in one study. *Enterobacter* spp. (45 isolates), *Pseudomonas* spp. (75 isolates) and *A. baumannii* (37 isolates) had fosfomycin susceptibility rates of 93, 44 and 35 %, respectively, in another study. Fosfomycin had good in vitro activity against ESBL-producing *Enterobacteriaceae.* For example, against ESBL-producing E. coli (522 isolates), fosfomycin had susceptibility rates of 86–100 %. ESBL-producing *E. coli* resistance rates against fosfomycin were 0–2.2 % with an MIC_{90} of 32 ug/mL. Against ESBL-producing *K. pneumoniae* (249 isolates), fosfomycin was 57.6-100% susceptible, with higher susceptibility rates than nitrofurantoin, ciprofloxacin or cotrimoxazole. The susceptibility of S. saprophyticus to fosfomycin varied by region, with a susceptibility rate of 100.0 % seen in a Greek study, compared with only 20.6 % in a Spanish study. For other Gram-positive organisms, *E. faecalis* had a fosfomycin susceptibility rate of 91.8 % (74 isolates). Susceptibility of *Enterococcus faecium* to fosfomycin varied by region with a susceptibility rate of 0 % in a Greek study (12 isolates) and a resistance rate of 0 % in a Turkish study (33 isolates).

Some of the bacterial isolates listed in the EUCAST fosfomycin document are rare or uncommon uropathogens. These should be excluded from the PI for this reason and also because antimicrobial susceptibility data is based on a low number of strains and so is subject to large varaibility and hence inaccuracy.

Comment: Based on all of the above data, the evaluator recommends the following changes to the proposed PI.

Commonly susceptible species: Escherichia coli Proteus spp. Klebsiella spp Citrobacter spp. Staphylococcus aureus *Enterococcus faecalis*
Species in which resistance may be a problem: Staphylococcus saphrophyticus Pseudomonas aeruginosa Enterobacter spp Serratia marcescens Morganella morganii Providencia spp Stenotrophomonas maltophilia *Enterococcus faecium*
Inherently resistant species: Acinetobacter spp. *Bacteroides spp and other anaerobic bacteria*

4.2.4. Pharmacodynamic effects

4.2.4.1. Primary pharmacodynamic effects

There is limited pharmacodynamic data available for fosfomycin. This is due to its preclinical development in the 1980s prior to the advent of antimicrobial pharmacodynamics. The drug was developed prior to recommendation by the Infectious Diseases Society of America that all new antimicrobials undergo pre-clinical pharmacodynamic studies including testing for presence or absence of the postantibiotic effect (Beam TR 1992). There are no good human or animal pharmacodynamic studies and very limited in vitro data. The nonclinical summary provided by the Sponsor contains the following information:

Fosfomycin is rapidly bactericidal at concentrations close to the MIC (Albini et al., 1986a; Cornaglia et al., 1988; Gismondo et al., 1986; Greenwood, 1986a; Lerner et al., 1988; Pinasi et al. 1987a; Ravizzola et al., 1987; Schito et al., 1993).

These studies are all published in the 1980s or early 1990s.

Due to the paucity of in vivo PD data, I have searched the literature. There are no in vivo studies apart from the early study by Carlone (1987) There are two in vitro studies I located which require consideration as a surrogate for the missing in vivo data (Utsui Y 1986) (Mazzei 2006) The study by Mazzei has been reviewed as it is clinically relevant.

The study by Mazzei (Mazzei 2006) is an in vitro study. It is the only study located on literature search for assessment of the postantibiotic effect of fosfomycin. The postantibiotic effect is an important PD parameter to assess when considering the dosage schedule of an antimicrobial agent. Mazzei studied the in vitro killing activity of varying concentrations of fosfomycin against 2 clinical isolates of *E. coli* and 2 isolates of *P. mirabilis* over a 24- hour period. Fosfomycin demonstrated a concentration-dependent bactericidal effect against the 4 strains, although a relatively high concentration was needed for *P. mirabilis* compared to *E coli*. At concentrations ≥8×MIC, there was no re-growth for more than 24 h for any of the 4 strains. Against both bacterial species, fosfomycin demonstrated a long concentration-dependent PAE of up to 4.7 hours.

The study by Utsui (1986) is an in vitro study of the bactericidal activity of two antibiotics including fosfomycin alone and in combination against 2 strains of methicillin-resistant S aureus (MRSA). Fosfomycin did not inhibit the growth of MRSA at a concentration of 0.25 MIC, but at 2xMIC, activity was bactericidal (Utsui, 1986). Higher concentrations and methicillin-susceptible S aureus (MSSA) strains were not tested. This study is of minimal clinical significance due to the very low concentrations tested.

The study by Wiedemann (1987) employs an in vitro PK model in which fosfomycin showed concentration-dependent killing against Enterobacter cloacae, E coli, and S aureus. Concentration-dependent killing also occurred for E faecalis, but only at the 3g dose. At lower doses (1g or less), fosfomycin was bacteriostatic against E faecalis. For all strains, a dosage of 3g was optimal as it also prevented regrowth of E cloacae, E coli, S aureus and E faecalis within 23 hours after the dose. Lower doses of fosfomycin (1g or less) did not prevent bacterial regrowth in all 4 species within the 23 hour window.

Comment: There is limited data available, but the studies by Mazzei (2006) and Wiedemann (1987) shows that fosfomycin has a concentration-dependent bactericidal effect in vitro against three species of Enterobacteriaceae (E coli, P mirabilis and Enterobacter cloacae) and a long in vitro postantibiotic effect against E coli and P mirabilis. The drug was much less active aginst E faecalis and for this organism, at lower concentrations was bacteriostatic rather than bactericidal. Against S aureus, the drug has not been well-studied but was bactericidal in the study by Wiedemann (1987) although less so than were the Enterobacteriaceae.

The proposed Australian PI states that "Limited data indicate that fosfomycin most likely acts in a time-dependent manner. "This is incorrect based on my evaluation of the data above. Suggest ask the non-clinical evaluator if there were any relevant studies that would assist in clarifying this further. If not, suggest reword PI to "Limited data indicate that fosfomycin most likely acts in a concentration-dependent manner."

Bergan (1990) studied 8 healthy male volunteers who received a dose of 25 mg/kg and after a washout period 50 mg/kg of fosfomycin trometamol. Urine samples were collected for up to 48 hours post-dose and the antibacterial effect of the patient's urine at different urinary dilutions was assessed. Bacteriostasis was assessed as lack of bacterial growth from urine at 48 hours. Reference strains of *E coli, Proteus mirabilis, Pseudomonas aeruginosa* and *Strep* (now called

Enterococcus) faecalis were studied. MICs of these strains were not listed. This study shows that urinary concentrations of fosfomycin were very high and at a dose of 50 mg/kg were sufficient to inhibit bacterial growth at 48 hours in urine diluted 256 times for E coli, 32 times for *Proteus mirabilis,* 64 times for *P aeruginosa,* and 8 times for *E faecalis.*

Carlone (1987) assessed the adhesive properties of fosfomycin pre-treated bacteria isolated from the urine of patients with UTIs gainst human urinary epithelial cells from a healthy volunteer. Norfloxacin and cotrimoxazole were also studied. Strains used were *P mirabilis (2), E coli (8), E faecalis (3*) and *Strep agalactiae (3).* Antimicrobials were added at concentrations of 1/4 and 1/8 of the MIC. All three antimicrobials reduced the adhesion of bacteria to the human epithelial cells, particularly at the higher concentration (1/4 MIC). Fosfomycin was as effective as norfloxacin against Gram-positive and Gram-negative bacteria and was more effective than cotrimoxazole at reducing bacterial adhesion.

4.2.4.2. Secondary pharmacodynamic effects

No studies presented.

The pivotal efficacy and safety study US-MON-03 excluded patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. This was not an exclusion criterion in the earlier related pivotal studies US-MON-01 and US-MON-02. Presumably this is because the activity of fosfomycin is altered in the presence of glucose-6-phosphate. There is no other information presented regarding this possible secondary pharmacodynamic effects in the dossier. Neither the proposed Australian PI nor the current American PI lists G6PD deficiency as a precaution or a contraindication.

Comment: Is the Sponsor aware of any theoretical or actual secondary pharmacodynamic effects of fosfomycin in glucose-6-phosphate dehydrogenase deficient patients? Why was G6PD deficiency an exclusion criterion in the study US-MON-03?

4.2.4.3. Relationship between drug concentration and pharmacodynamic effects

Data in this area is extremely limited and is based on a small amount of in vitro data only. A dose of 3g fosfomycin trometamol appears optimal in terms of bactericidal activity and resistance development. A dose of 1g fosfomycin trometamol was inferior. Higher doses or sequential dosing have not been studied.

The PK/PD parameters of safety and the PK/PD parameters and breakpoints of efficacy for fosfomycin have not been studied in vitro or in vivo and are unknown.

The plasma concentration-effect curves have not been defined for the primary PD effect. The therapeutic window has not been defined in terms of plasma concentrations of the drug.

The dose regimens used in the pivotal clinical trials were not based on plasma-concentration effect data.

The plasma concentrations of the drug have not been correlated with efficacy or safety outcomes.

4.2.4.4. Fosfomycin resistance development

The dossier contains very limited information on fosfomycin resistance development. Important considerations are the epidemiology of fosfomycin resistance and any relationship to fosfomycin usage patterns, and also the cellular and genetic mechanisms of bacterial resistance development and how easily these occur.

4.2.4.5. Epidemiology of fosfomycin resistance development and its relationship to fosfomycin usage

Fosfomycin was initially approved for usage in some European countries in the 1980s and by the 1990s had approvals in many countries particularly in Europe but also elsewhere. The

PSURs contained in the dossier show that sales in some European countries such as Spain were as high as 500,000 treatment doses per year. What has been the effect of fosfomycin usage on fosfomycin resistance patterns?

The study by Junquera et al (2005) examined the changes in resistance patterns in *E coli* isolated from urine cultures for several antimicrobials during the period 1994-2001. Isolates were those sent to a hospital microbiology laboratory in Madrid Spain. There were 14,319 urinary isolates of E coli during the 8-year period. From 1996, the isolates were stratified as either hospital-acquired (10,913 isolates) or community-acquired (2350 isolates). Isolates were tested using NCCLS guidelines and breakpoints. Of note is that susceptibility to fosfomycin remained high during the 8 year period with 99% susceptible in 1994 (1056 isolates) and 98.4% susceptible in 2001 (1666 isolates). When results were stratified by hospital or community or health-care facility acqusition, no differences were noted in susceptibility.

This study shows that in one centre acrosss an 8-year period, excellent fosfomycin susceptibility to E coli was maintained. What then were the usage rates for fosfomycin in Spain in the period 1994-2001? The drug was first approved for usage in Spain in November 1990 (PSUR 1 Jan 1995-31 Dec 1999). No data or commentary was provided in the publication by Junquera, which did not attempt to correlate resistance development with specific antimicrobial usage. I have attempted to do so based on some information available in the dossier.

The PSURs provided by Zambon are contained in the dossier and give worldwide sales figures for Monurol in Spain. 307,000 units were sold in 1995 increasing to 455,000 by 1999 (PSUR 1 Jan 1995-31 Dec 1999, p10). The licensed indication in Spain at that time was a single dose of fosfomycin for the treatment of UTI. This suggests approximately 300,000 - 450,000 doses of fosfomycin were sold (and presumably taken) each year in Spain during the surveillance period.

It is reassuring to note that no significant resistance development occurred for fosfomycin, at least in isolates from one microbiology laboratory, during this 8-year period despite high usage rates for the drug in the same country.

Table 7: *E coli* susceptibility in one hospital in Madrid, Spain during the 8 year period from 1994-2001 (from Juncquera et al, 2005)

[redacted] *Escherichia coli isolates susceptibility percentage during 8 years (1994 - 2001).*

Antibiotic	1994 (n=1056)	1995 (n=1829)	1996 (n=2034)	1997 (n=2050)	1998 (n=1963)	1999 (n=1750)	2000 (n=1971)	2001 (n=1666)	χ^2 (p)	χ^2 TL(p)
Ampicillin/ amoxicillin	42.3	42.3	42.6	40.4	42.3	40.2	37.2	39.8	18.7 (0.009)	10.6 (0.001)
Ampicillin-sulbactam	87.5	86.2	91.1	92.7	-	-	-	-	261.5 (<0.0001)	212.5 (<0.0001)
Amoxicillin-clavulanic acid	-	-	-	-	96.0	96.3	97.2	96.9	91.3 (<0.0001)	56.8 (<0.0001)
Ticarcillin	42.6	42.6	42.9	40.4	42.7	39.1	37.5	40.8	22.1 (0.002)	10.4 (0.001)
Cefazolin	96.4	94.6	95.1	95.8	96.6	95.9	95.4	95.9	13.1(NS)	0.94(NS)
Cefuroxime	98.3	96.5	96.6	95.6	96.5	97.2	96.4	96.7	21.5 (0.003)	11.2 (0.001)
Cefotaxime	100.0	99.6	99.9	99.1	98.6	99.0	98.5	98.5	51.8 (<0.0001)	41.4 (<0.0001)
Ceftazidime	99.6	99.0	99.6	98.5	98.2	98.3	97.5	97.8	53.1 (<0.0001)	41.7 (<0.0001)
Gentamicin	94.6	94.5	93.5	92.1	92.7	93.6	93.4	93.0	14.03 (NS)	2.95 (NS)
Amikacin	100.0	99.9	99.8	99.9	99.8	99.9	99.8	99.8	64.9 (<0.0001)	4.02 (0.045)
Nalidixic acid	76.0	71.2	71.9	70.1	71.4	70.4	69.5	66.3	33.4 (<0.0001)	23.23 (<0.0001)
Norfloxacin	85.1	80.6	81.6	78.0	74.3	71.8	70.9	66.6	235.3 (<0.0001)	226.25 (<0.0001)
Cotrimoxazol	67.9	63.3	64.2	67.5	70.2	65.3	66.3	66.2	17.4 (0.015)	7.59 (0.006)
Fosfomycin	99.0	98.7	98.9	98.5	97.6	98.2	97.9	98.4	28.05 (<0.0001)	1.18 (NS)
Nitrofurantoin	92.0	91.3	94.6	97.7	98.2	95.6	96.2	97.5	186.9 (<0.0001)	92.0 (<0.0001)

χ^2 TL: Pearson chi-square linearity test; n: number of *E. coli* isolates; χ^2 : Pearson chi-square test; NS: not significant

4.2.4.6. Mechanisms of fosfomycin resistance

Several chromosomal or plasmid-mediated mechanisms of fosfomycin resistance may occur, including target site modification and inactivation. The following information is obtained from Nonclinical overview section "Mechanisms of resistance and development of resistance". All the studies referred to in this summary are contained the dossier so should have been reviewed by the non-clinical evaluator.

I note the following excerpt: "Mechanisms of resistance and development of resistance". "Resistance to fosfomycin appears to be primarily due to chromosomal mutations (Borsotto et al., 1988; Courtieu et al., 1977; Ferrara et al., 1988; Llaneza et al., 1985; Rossi et al., 1988; Schito et al., 1993; Wiedemann and Groos, 1987) although plasmid mediated resistance has also been reported (Mendoza et al., 1980; Suarez and Mendoza, 1991). Spontaneous mutants resistant to fosfomycin have been obtained in vitro. They usually carry mutation on the chromosomal genes glpT and uhp, which control the transport of L-alpha-glycerophosphate and hexose phosphate, respectively (Borsotto et al., 1988; Ferrara et al., 1988; Rossi et al., 1988; Wiedemann and Groos, 1987). Several investigators determined the frequency of emergence of resistant variants to fosfomycin trometamol in the presence of different selecting concentrations in nutrient broth and in urine at different pH values (Courtieu et al., 1977; Ferrara et al., 1988; Rossi et al., 1988). Using E. coli as a model, Arca et al. 1988 showed that plasmid-bone resistance to fosfomycin in Gram-negative bacteria is due to the formation of an adduct between fosfomycin and glutathione. The responsible enzyme is glutathione S-transferase. Purification and characterization of this en-zyme has been accomplished (Arca et al., 1990) as the nucleotide sequence and intracellular lo-cation of the product of the fosfomycin resistance gene. The nucleotide sequence of the fosB gene conferring fosfomycin-resistance in S. epidermidis was sequenced, and was not closely related to fosA, which codes for fosfomycin resistance in Enterobacteriaceae (Zilhao and Courvalin, 1990). Rossi et al. (1988) found that all spontaneous mutants selected in the presence of 150 mcg/ml of fosfomycin were susceptible to 1000 and

2000 mcg/ml of fosfomycin. Greenwood (1986a) evaluated the response to fosfomycin trometamol of four strains of E. coli in an in vitro bladder model in which the hydrokinetic aspects of the treatment of bacterial cystitis can be simulated. Two strains of E. coli that were fully susceptible to fosfomycin and a strain of intermediate susceptibility responded well to relatively low concentrations: doses achieving peak concentrations of 50 to 250 mcg/ml suppressed. Mendoza et al. (1980) first described the isolation of plasmids conferring resistance to fosfomycin from clinical isolates of S. marcescens. Unlike transport mutants, these isolates were quite capable of incorporating the drug, and they have a fully sensitive enolpyruvyl transferase, the molecular target of fosfomycin. Schito et al. (1993) determined the susceptibility of several species of bacteria to fosfomycin. The overall rate of resistance to fosfomycin was 1% for Gram-positive bacteria and 1.8% among Gram-negative organisms. Cross-resistance of fosfomycin to other classes of antimicrobial agents has not been obeserved in many laboratories (Ferrara et al., 1988; King and Philips 1988; Schito et al., 1993)."

The dossier contains no studies of mechanisms of fosfomycin resistance development. It does contain the review paper by Keating (2013) which contains an excellent summary of the paper of knowledge of potential mechanisms of resistance to that time in 2013. On reading this review paper, I noted that the summary of fosfomycin resistance mechanisms and development was old data with no publication later than 1993. In particular, the publications in the paper by Keating (Karageorgopoulos et al, 2012; Marchese et al, 2003; Nilsson et al, 2003; Oteo et al, 2009; Rodriguez-Avial et al, 2013; Oteo et al, 2010) are not located in the dossier and not referred to in the summaries. Additionally, the review paper by Michalopoulos (2011) has a small section entitled "Mechanism of fosfomycin resistance". The references in this section (Beharry et al, 2005; Horii et al, 1999; Garcia et al, 1994; Cao et al, 2001; Bernat et al, 1997; Rigsby et al, 2005; Arca et al, 1997) are not included for review. From reading the titles, these appear to be primarily nonclinical studies although the paper by Karageorgopoulos (2013) from the title appears to have a clinical and nonclinical component. If the nonclinical evaluator has not identified and evaluated these more recent studies of mechanisms and development of resistance development, the Sponsor will need to provide an accurate current summary of this area (as the summary is more than 20 years out of date) and in particular provide the papers referred to above for review by either of the evaluators, as appropriate.

The dossier contains a document entitled "Fosfomycin: risk assessment of microbial assessment". This is a current review paper about the development of fosfomycin resistance, the genetics of resistance and the ease of development of resistance. The paper lists 52 references. The most recent is dated 1988. None of the other 48 references referred to in this review paper have been submitted to the TGA for review. Clearly this is either an oversight or a planned omission of material from the dossier. This important area requires detailed review by the TGA.

Comment: The Sponsor has not included any studies of fosfomycin resistance development and mechanisms from 1994 onwards. At least 13 studies were identified easily from two review papers and 48 other papers from the review paper. This is a serious omission from the dossier. Has the Sponsor taken care to update the dossier and ensure it is current since approval of fosfomycin by the FDA in 1996 and Canada in 1999? A current review of resistance development and mechanisms is critical to the approval process of any antimicrobail agents. Please ask the Sponsor to provide the studies above and any other relevant studies published in the last 20 years for review by the reviewers, as appropriate.

4.2.4.7. Pharmacodynamic studies of fosfomycin resistance development

The dossier contains two pharmacodynamics studies of resistance development, both published in 1987. The study by Greenwood (1987) examines the activity of 2 fosfomycin-susceptible and 2 fosfomycin-resistant *E coli* strains in an in vitro dynamic bladder model. The broth used was glucose-6-phosphate deficient Eugonbroth as urine does not contain glucose-6-phosphate (and supplemental glucose-6-phosphate is known to increase the activity of fosfomycin, see

"Mechanism of Action". To assess bacterial resistance development, surviving bacteria after a cycle were re-exposed to a second identical drug dose after bacterial regrowth had occurred. For the two fosfomycin-susceptible strains, when the peak concentration achieved was 50 or 250 mg/L, bacterial growth was suppressed for 20 hours or more, but a second dose had reduced effect and resistance readily emerged. When the peak concentration was 2500 mg/L, resistance did not develop. The two fosfomycin-resistant strains behaved differently to each other. One with MIC 64 mg/L responded almost as well as the fosfomycin-susceptible strains, and no increase in resistance occurred after exposure to the 2500 mg/L concentration. The other strain with MIC 128 mg/L failed to respond to the lower doses. It suppressed growth at the 2500 mg/L dose for 22 hours but for a lesser time of 11 hours after the 2nd dose. Neither of the two initially fosfomycin-resistant strains had MICs repeated at the end of the experiment. This would have been of interest and some importance to see if MIC had risen substantially.

The study by Wiedemann (1987) is primarily an in vitro pharmacodynamic study. However, it does contains some resistance development data. Bacterial strains which eventually regrew after fosfomycin exposure had their MICs assessed to look for resistance development. These strains were compared to the MIC of strains prior to fosfomycin dosing. At the 3g dose, MICs remained essentially unchanged. At the lower dosages (1g or less), MICs increased substantially for *K pneumoniae, E cloacae* and *E faecalis* ie resistant mutants developed.

This is some interest currently in the concept of mutant selection windows (MSWs) and mutant prevention concentrations (MPCs) for fosfomycin. Recent publications are conducted in vitro or in tissue cage models so should have been included for review.

Comment: Could the Sponsor provide the following studies for review, as appropriate (if not already reviewed):

Mei Q, Ye Y, Zhu YL, et al. "Testing the mutant selection window hypothesis in vitro and in vivo with Staphylococcus aureus exposed to fosfomycin" Eur J Clin Microbiol Infect Dis. 2015 Apr;34(4):737-44

Liu LG, Zhu YL, Hu LF, et al. Comparative study of the mutant prevention concentrations of vancomycin alone and in combination with levofloxacin, rifampicin and fosfomycin against methicillin-resistant Staphylococcus epidermidis. J Antibiot (Tokyo). 2013 Dec;66(12):709-12.

PSUR1 Aug 2015-31 Jan 2016 refers to a pre-clinical study which started in May 2015 for the in vitro evaluation of the MPC (mutant prevention concentration) and the MSW (mutant selection window) of fosfomycin on Gram negative bacterial strains (*Escherichia Coli, Proteus Mirabilis* and *Klebsiella Pneumoniae*). It states that "the first available results show a powerful bactericidal activity of fosfomycin if the starting concentrations are kept higher than MPC values for some hours. In this case a second growth occurs after 24 hours and no resistance event is observed: a second dose is beneficial. On the contrary, if the starting concentration peak is not higher than MPC value, a second growth is faster and the bacteria are resistant; in this case a second dose is useless. The successful treatment (one or two administrations) is relative to the strain involved in the infection. Further experiments are ongoing at the time of this report".

Comment: This study appears to be unpublished on literature search in Oct 2016. Is the Sponsor able to provide study results, for example conference presentations?

4.2.4.8. Effect of fosfomycin on bowel flora resistance patterns

Collateral damage, a term describing ecological adverse effects of antimicrobial therapy, such as the selection of drug-resistant organisms and colonization or infection with multidrug-resistant organisms, has been associated with use of broad-spectrum cephalosporins and fluoroquinolones. Uncomplicated UTI is one of the most common indications for antimicrobial exposure in an otherwise healthy population; very small increments in collateral damage repeated many times may in aggregate magnify the impact of collateral damage when it occurs.

Hence, in any new antimicrobial evaluation, the effect of the antimicrobial on body bacterial flora must be considered. The dossier contains only one study evaluating this. The study by Gupta et al (2005) considers the relative effect of fosfomycin, nitrofurantoin and ciprofloxacin on the antibiotic susceptibility patterns of microbial bowel flora. This study examines the bowel flora of women after treatment of acute uncomplicated lower UTI. *E coli* was the uropathogen in 77% of cases. Rectal colonisation with *E coli* was present in 94% of women at baseline. There was a significant reduction in the prevalence of rectal E. coli after treatment with ciprofloxacin and fosfomycin, but not after treatment with nitrofurantoin ($P < 0.001$). By study visit 4 (day 28-30 after therapy), rectal prevalence of E coli had returned to baseline for fosfomycin patients but not for ciprofloxacin patients. All rectal E. coli strains isolated from the subjects in the nitrofurantoin and fosfomycin treatment groups were susceptible to the study drug with which the subject had been treated. One of 25 women in the ciprofloxacin group had isolation of fluoroquinolone-resistant rectal *E. coli.*

Comment: Data in this area is limited, but it appears from this one small study that the effect of fosfomycin on prevalence of *E coli* in bowel flora is comparable to nitrofurantoin and less than ciprofloxacin. *E coli* resistant to study drug occurred in 1/25 ciprofloxacin patients but none of 17 nitrofurantoin and 20 fosfomycin patients.

4.3. Evaluator's overall conclusions on pharmacodynamics

4.3.1. Summary of pharmacodynamics

4.3.1.1. Mechanism of action

- Fosfomycin is a phosphonic acid antibiotic which acts on the first stage of bacterial cell wall synthesis.
- Fosfomycin inhibits the enzyme phosphoenolpyruvate UDP-GlcNac-3-enolpyruvyl transferase which is contained in the bacterial cell wall. This irreversibly blocks the condensation of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate.
- Fosfomycin is actively transported into the bacterial cell wall via two different transport systems. These are the L-alpha-glycerophosphate transport system or alternatively the hexose phosphate pathway.
- The activity of fosfomycin is augmented in the presence of glucose-6-phosphate.
- Fosfomycin acts at a different stage of cell wall synthesis than the beta-lactam antibiotics. It mechanism of action is unique and therefore cross-resistance with other antibiotics in unlikely.

4.3.1.2. Antimicrobial susceptibility testing

- Fosfomycin trometamol is not calibrated for antimicrobial susceptibility testing against many bacteria, according to current clinical microbiology guidelines.
- Using EUCAST methods and breakpoints, fosfomycin trometamol single 3g oral dose is calibrated for the treatment of acute uncomplicated UTIs caused by Enterobacteriacae genus (this genus of aerobic gram negative bacteria includes E coli, Proteus mirabilis, Klebsiella, Serratia etc). MIC breakpoints are <32 mcg/ml (susceptible) and >64 mcg/ml (resistant).
- There are no EUCAST methods or breakpoints for other urinary pathogens such as *Pseudomonas, Staphylococcus saphrophyticus,* or *Enterococcus.*
- EUCAST methods that can be used are disc, gradient MIC strip, agar dilution, broth dilution or commercial systems. All methods must have additional glucose-6-phosphate supplementation.

- Using CLSI methods and breakpoints, only E coli and Enterococcus faecalis from urinary tract isolates are calibrated. Current MIC breakpoints for both are <64 mcg/ml (susceptible), 128 mcg/ml (intermediate), and >256 mcg/ml (resistant). Importantly, NO OTHER bacterial species apart from E coli and Enterococcus faecalis have susceptibility testing guidelines by CLSI methodology.
- Studies that report fosfomycin susceptibility for other bacterial species usually extrapolate breakpoints from known E coli breakpoints but this has not been validated.
- Disc and agar dilution CLSI methods are approved provided there is supplemental glucose-6-phosphate. CLSI does not recommend broth dilution fosfomycin susceptibility testing for fosfomycin.

4.3.1.3. Antimicrobial activity of fosfomycin

- Many of the studies of fosfomycin susceptibility contained in the dossier were performed studies when the drug was originally approved in Europe in the 1980s.
- In Australia, the drug has had limited availability on the SAS scheme only.
- Many Australian laboratories currently only test fosfomycin for urinary pathogens that are resistant to other oral antibiotics.
- A preclinical study of fosfomycin susceptibility performed in the United States prior to approval there in 1996 shows that E coli is usually susceptible, but there is some intrinsic resistance in Enterobacter, Morganella morganii, Providencia, Staph saphrophyticus, Pseudomonas , Enterococcus and Stenotrophomonas. Acinetobacter spp. was usually resistant.
- The Antimicrobial Resistance Epidemiological Survey on Cystitis (ARESC) Study included 9 European countries and Brazil. In 2008, their study of 4,264 adult women with acute uncomplicated lower UTI showed that E.coli was most frequent uropathogen (76.7%). E coli fosfomycin susceptibility was 98.1%. Only 0.6% of E coli isolates had an MIC of >128 mg/L.
- In the ARESC Study, the most common uropathogens after E coli were Klebsiella pneumoniae, Proteus mirabilis and Staphylococcus saphrophyticus, all of similar incidence at 3.4-3.6%. Fosfomycin resistance rates were 5.6% for Klebsiella pneumoniae and 9.7% for Proteus mirabilis, using an extrapolated CLSI breakpoint of >256 mg/L as resistant. Fosfomycin susceptibility could not be reported for Staph saphrophyticus as there are no known breakpoints.
- In a Taiwanese study published in 2011 of 960 bacteria associated with UTI, E coli was uniformly susceptible, and Klebsiella pneumoniae and Enterobacter cloacae were usually although not always susceptible. Pseudomonas and Stenotrophomonas susceptibility was highly dependent on whether CLSI or EUCAST breakpoints were used (extrapolated from E coli). Acinetobacter baumaniae was usually resistant. Fosfomycin was very active against Staphylococcus aureus (including methicillin-resistant strains) and E faecalis (including vancomycin-resistant strains). Activity against E faecium was very dependent on whether extrapolated CLSi or EUCAST breakpoints were used.
- There are no PK/PD breakpoints for fosfomycin.
- Bacterial species which are common uropathogens and are usually fosfomycin susceptible include E coli (most common uropathogen), Citrobacter spp, Klebsiella spp, Proteus spp, Enterococcus faecalis, and S aureus.
- Bacterial species which are not uncommon uropathogens and are frequently fosfomycin resistant include Enterobacter spp, Serratia marcescens, Morganella morganii, Providencia spp, Pseudomonas aeruginosa, Staph saphrophyticus, Stenotrophomonas maltophilia and Enterococcus faecium.

- Bacterial species which are not uncommon pathogens and are usually fosfomycin resistant include Acinetobacter spp.
- Fosfomycin has useful activity against many ESBL-producing isolates of E coli and Klebsiella pneumoniae.

4.3.1.4. Primary pharmacodynamic effects of fosfomycin

- There is very limited pharmacodynamic data available for fosfomycin due to its initial early preclinical development in the 1980s prior to the modern development of antimicrobial pharmacodynamics.
- There are no good human or animal model studies of the pharmacodynamics of the drug and very limited in vitro data.
- Fosfomycin is rapidly bactericidal at concentrations close to the MIC.
- In an in vitro study, fosfomycin demonstrated a concentration-dependent bactericidal effect against P. mirabilis and E coli. At concentrations≥8×MIC, there was no re-growth for more than 24 h. Against both bacterial species fosfomycin demonstrated a long concentration-dependent PAE of up to 4.7 hours.
- In an in vitro PK model, fosfomycin showed concentration-dependent killing against Enterobacter cloacae, E coli, and S aureus. Concentration-dependent killing also occurred for E faecalis, but only at the highest 3g dose. At lower doses (1g or less), fosfomycin was bacteriostatic against E faecalis. For all strains, a 3g dosage prevented regrowth of E cloacae, E coli, S aureus and E faecalis within 23 hours after the dose.
- Suggest reword proposed PI to "Limited data indicate that fosfomycin most likely acts in a concentration-dependent manner".
- In a study of 8 healthy male volunteers who received a dose of 50 mg/kg of fosfomycin, urinary concentrations of fosfomycin were very high and this dose was sufficient to inhibit bacterial growth at 48 hours in urine diluted 256 times for *E coli*, 32 times for *Proteus mirabilis,* 64 times for *P aeruginosa,* and 8 times for *E faecalis.*
- In a study of the activity of fosfomycin pre-treated bacteria (*P mirabilis, E coli, E faecalis* and *Strep agalactiae*) isolated from the urine of patients with UTIs tested against human urinary epithelial cells, fosfomycin reduced bacterial adhesion.

4.3.1.5. Secondary pharmacodynamic effects

- No studies presented.
- Fosfomycin activity is augmented in the presence of glucose-6-phosphate and G6PD deficiency is an exclusion criteria in the most recent of the pivotal studies (US-MON-03). Is the Sponsor aware of any theoretical or actual secondary pharmacodynamic effects of fosfomycin in G6PD deficient patients? Why was G6PD deficiency an exclusion criterion in the study US-MON-03?

4.3.1.6. Time course of pharmacodynamic effects

- No studies.

4.3.1.7. Relationship between drug concentration and pharmacodynamic effects

- Data in this area is extremely limited and is based on a small amount of in vitro data only.
- A dose of 3g fosfomycin trometamol appears optimal in terms of bactericidal activity and resistance development (see this section below). A dose of 1g fosfomycin trometamol was inferior. Higher doses or sequential dosing has not been studied.

- The PK/PD parameters of safety and the PK/PD parameters and breakpoints of efficacy for fosfomycin have not been studied in vitro or in vivo and are unknown.

4.3.1.8. Genetic, gender and age related differences in pharmacodynamic response

- No studies.

4.3.1.9. Pharmacodynamic interactions

- No studies.

4.3.1.10. Epidemiology of fosfomycin resistance development and its relationship to fosfomycin usage

- In a study of 14,319 urinary isolates of E coli in Spain, fosfomycin susceptibility was 99% in 1994 and 98.4% in 2001. Fosfomycin susceptibility to E coli was maintained despite sales of 307,000 doses of fosfomycin in Spain in 1995 increasing to 455,000 by 1999.

4.3.1.11. Mechanisms of fosfomycin resistance

- Chromosomal or plasmid-mediated mechanisms of fosfomycin resistance may occur, including target site modification and inactivation.
- All resistance mechanism papers were published in 1993 or earlier and the resistance mechanisms summary provided by the Sponsor also does not reference any studies later than 1993. Review papers reference at least 13 papers on the resistance mechanisms of fosfomycin published since 1994. These papers should have been included in the dossier but were not.
- The resistance development data in the dossier is more than 20 year out of date. If the nonclinical evaluator has not identified this deficiency and reviewed the missing papers, please ask the Sponsor to provide a more recent summary of resistance mechanisms and provide any relevant papers including but not limited to the 13 papers discussed above. Also please provide for review all 48 publications referred to in the review paper "Fosfomycin: risk assessment of microbial resistance".

4.3.1.12. Pharmacodynamic studies of fosfomycin resistance development

- In an in vitro dynamic bladder model, surviving bacteria after a 3g dosage of fosfomycin were re-exposed to a second identical drug dose after bacterial regrowth had occurred. For two fosfomycin-susceptible strains, when the peak concentration achieved was 50 or 250 mg/L, bacterial growth was suppressed for 20 hours or more, but a second dose had reduced effect and resistance readily emerged. When the peak concentration was 2500 mg/L, resistance did not develop.
- This is some interest currently in the concept of mutant selection windows (MSWs) and mutant prevention concentrations (MPCs) for fosfomycin. There are at least 3 recent in vitro studies published but not included. If the evaluator has not reviewed these, could the Sponsor provide these for review please? Also, has the MPC and MSW study referred to in PSUR1 Aug 2015-31 Jan 2016 refers to a pre-clinical study started in May 2015 for the in vitro evaluation of the MPC (mutant prevention concentration) and the MSW (mutant selection window) of fosfomycin on Gram negative bacterial strains (Escherichia Coli, Proteus Mirabilis and Klebsiella Pneumoniae). It states that "the first available results show a powerful bactericidal activity of fosfomycin if the starting been published? Is the Sponsor able to provide this for review?

4.3.1.13. Effect of fosfomycin on bowel bacterial flora

- What is the relative effect of fosfomycin on bowel bacterial flora in comparison to other antibiotics? In a study of women after antibiotic treatment for acute uncomplicated lower UTI, rectal colonisation with E coli was present in 94% of women prior to treatment. There

was a significant reduction in the prevalence of rectal E. coli after treatment with ciprofloxacin and fosfomycin, but not after treatment with nitrofurantoin. By day 28-30 after therapy, rectal prevalence of E coli had returned to baseline for fosfomycin patients but not for ciprofloxacin patients. All rectal E. coli strains isolated from the subjects in the nitrofurantoin and fosfomycin treatment groups were susceptible to the study drug with which the subject had been treated. One of 25 women in the ciprofloxacin group had isolation of fluoroquinolone-resistant rectal E. coli.

4.3.2. Limitations of PD studies

- There is very limited pharmacodynamic data available for fosfomycin as its preclinical development in the 1980s predated the advent of antimicrobial pharmacodynamics.
- There are no known PK/PD breakpoints for fosfomycin.
- Fosfomycin susceptibility testing methods and breakpoints only exist for Enterobacteriaceae (includes E coli) and Enterococcus faecalis.
- There is only one study of the effect of fosfomycin on bowel bacterial flora.
- There are no publications on fosfomycin resistance development and mechanisms that are more recent than 1993. There are a large number of studies in this area that have not been included in the dossier. These will require review if not already done so as an integral component of any possible approval process.

4.3.3. Questions regarding the PD studies

- Is the Sponsor aware of any theoretical or actual secondary pharmacodynamic effects of fosfomycin in glucose-6-phosphate dehydrogenase deficient patients? Why was G6PD deficiency an exclusion criterion in the study US-MON-03?
- The Sponsor has not included any studies of fosfomycin resistance development and mechanisms from 1994 onwards. At least 13 studies were identified easily from two review papers. These studies are the references in the paper by Keating (Karageorgopoulos et al, 2012; Marchese et al, 2003; Nilsson et al, 2003; Oteo et al, 2009; Rodriguez-Avial et al, 2013; Oteo et al, 2010) and the references in the paper by Michalopoulos (2011) (Beharry et al, 2005; Horii et al, 1999; Garcia et al, 1994; Cao et al, 2001; Bernat et al, 1997; Rigsby et al, 2005; Arca et al, 1997). The lack of recent studies on resistance mechanisms and development is a serious omission from the dossier. Has the Sponsor taken care to update the dossier and ensure it is current since approval of fosfomycin by the FDA in 1996 and Canada in 1999? A current review of resistance development and mechanisms is critical to the approval process of any antimicrobial agents. Please ask the Sponsor to provide the studies above and any other relevant studies published in the last 20 years for review by the reviewer, as appropriate.
- Could the Sponsor provide the recent studies on mutant selection windows and mutant prevention concentrations for review to the evaluator, as approriate (if not already reviewed by the evaluator)? The studies are Mei Q, Ye Y, Zhu YL, et al. Eur J Clin Microbiol Infect Dis. 2015 Apr;34(4):737-44 ; Liu LG, Zhu YL, Hu LF, et al. J Antibiot (Tokyo). 2013 Dec;66(12):709-12; Pan AJ, Mei Q, Ye Y, et al. J Antibiot (Tokyo). 2016 Oct 19 epub; and the unpublished study if results are available referred to in PSUR1 Aug 2015-31 Jan 2016.

5. Dosage selection for the pivotal studies

A single 3g fosfomycin trometamol sachet (Monurol or Monuril) was used in all 3 pivotal studies and the vast majority of all the clinical trials. Some of the early trials used a 2g sachet in adolescent females but there is limited PK data to support this.

5.1. Evaluator's conclusions on dose finding for the pivotal studies

There were no good dose-finding pivotal studies performed. This is because the dose of 3g single oral dose had been well-established in many nonpivotal efficacy studies described, which predated the 3 pivotal efficacy studies described.

A single 3g oral sachet appears an appropriate dose in all females 12 years and over with normal to moderately impaired renal function based on the PK and limited PD data available.

6. Clinical efficacy

6.1. Studies providing evaluable efficacy data for Indication 1

Pivotal efficacy studies

- Study MON-US-01 (Kraus, 1994)
- Study MON-US-02 (Harnack, 1994)
- Study MON-US-03 (Bowman 1996)

Nonpivotal efficacy studies

- Boerema et al, 1988
- Richaud, 1989
- Asscher, 1991
- Boerema and Groeneveld, 1987
- Van Pienbrook et al, 1993
- Selvaggi, 1990
- Pontonnier, 1988
- Reynaert, 1988
- Dejonckheere, 1988
- Jardin, 1987
- De Caro, 1984
- Di Nola, 1984
- Krejci 1994
- Marini 1984
- Moroni, 1984
- Moroni, 1987a
- Rizzo, 1984
- Rolandi, 1984
- Study Group Switzerland, 1989
- Krcmery, 2001
- Usta, 2011

- Ferreira, 2003
- Ferraro, 1990
- Pullukcu et al, 2007
- Senol, 2010
- Neuman, 1987

6.2. Pivotal efficacy studies for Indication 1

6.2.1. Study ID MON-US-01 [Kraus 1994]

6.2.1.1. Study design, objectives, locations and dates

This was a phase 3, prospective, parallel, multicentre, double-blind, double-dummy randomised safety and efficacy study of female patients with acute uncomplicated lower UTI. The primary objective of the study was to compare the efficacy of a single oral dose of fosfomycin tromethamine (3 g single dose sachet) to oral ciprofloxacin 250 mg every 12 hours for ten days, in female patients with uncomplicated lower UTI. The secondary objective was to compare the safety profile of fosfomycin tromethamine to that of ciprofloxacin.

The study was conducted between January 1991 and April 1993 in 34 centres in the United States (32 of 34 sites enrolled patients). Centres enrolled between 1 and 74 patients, with 12 study centres enrolling 15 or more patients per treatment group.

6.2.1.2. Inclusion and exclusion criteria

Inclusion criteria were all 3 of the following:

- female patients aged 18 years or older;
- mandatory symptoms of a UTI (defined as dysuria, frequency and / or urgency) with onset of symptoms <48 hours (January – March 1991) or <96 hours (March 1991-April 1993); and
- one or more positive pre-treatment urinary culture (defined as >105 CFU of at least one uropathogen /mL urine) collected by clean-voided midstream catch method within 48 hours of enrolment.

Important exclusion criteria were any of the following: known or suspected structural abnormalities of the urinary tract (eg calculi, stricture); primary renal disease; neurogenic bladder; pregnancy (excluded by pregnancy test in women of child-bearing age); lactation; patients with recurrent UTIs (defined as greater than 3 UTIs within the preceding year); patients who had received treatment with other antimicrobials within 48 hours prior to entry into the study; symptoms and/ or signs suggestive of upper UTI (fever > 101 degrees F, flank pain, chills); severe renal impairment (estimated creatinine clearance <30 ml/min; patients who received theophylline, probenecid. or metoclopramide; patients with known or suspected CNS disorders which would predispose the patient to seizures; patients with acute symptomatic vaginitis; immunosuppression or neutropenia; and patients unlikely to present for follow-up.

Patients with indwelling urinary catheters were allowed but in practice none were enrolled. In March 1991, the clinical criterion for enrolment was amended to allow patients with <96 hours of clinical signs or symptoms rather than <48 hours of symptoms or signs. At the same time, an additional exclusion criterion was added of prohibiting analgesics or antispasmodics within 96 hours prior to enrolment and during the trial.

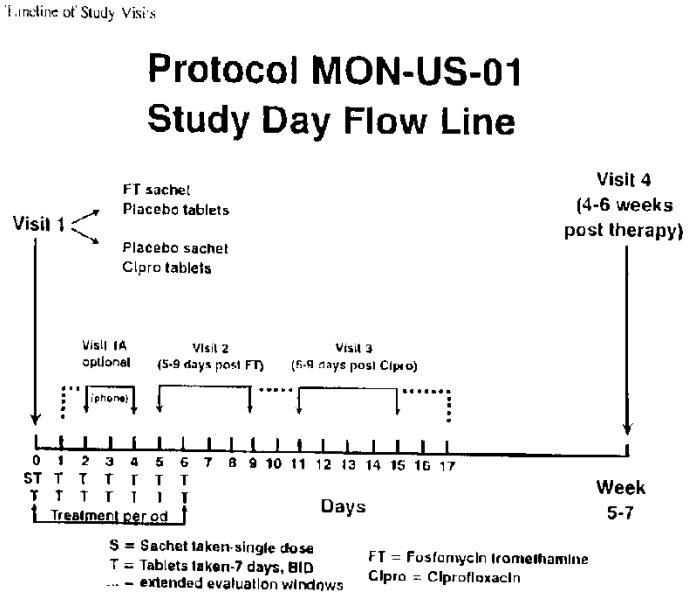
6.2.1.3. Study treatments

Oral fosfomycin trometamol 3g as a single oral dose was compared to oral ciprofloxacin 250 mg twice-daily for 7 days. All patients received either a single fosfomycin or placebo sachet at study

entry followed by one 250 mg ciprofloxacin or placebo tablet twice daily for 7 days. Each group received one active drug and one placebo.

The study schematic is shown below.

Figure 2: Study schematic of Study MON-US-01



Concomitant medication: Antacids could not be taken for 2 hours prior to or following a dose of medication (potential ciprofloxacin interaction), but there was no mention of other cations which could interact with ciprofloxacin, for example iron, calcium or magnesium tablets.

6.2.1.4. Efficacy variables and outcomes

The primary efficacy variables were bacteriological and clinical efficacy.

Bacteriological efficacy was defined as baseline positive midstream urine collection culture (MSU) (defined as $>10^5$ CFU/mL urine of at least one uropathogen) taken within 48 hours of enrolment, followed by levels of the same uropathogen reduced to levels $<10^4$ CFU/mL MSU culture collected at visit 2 for fosfomycin (days 5-11) or visit 3 for ciprofloxacin (day 11-17). Note that all patients had cultures collected at visits 2 and 3 as the study was blinded.

The other important efficacy variable was clinical efficacy, defined as resolution or improvement in typical UTI symptoms (flank tenderness, suprapubic tenderness, dysuria, urinary urgency, urinary burning and urinary frequency) scored on a four-point scale (0=absent to 3=severe) by the blinded investigator at baseline and repeated at visits 2 and 3. The possible outcomes were: cure, improvement, failure, and not assessable. These were defined as:

- Cure: All pre-therapy signs and symptoms had subsided in a reasonable period of time with no evidence of their resurgence at the follow-up visit 5-11 days after the first/last dose of fosfomycin, or 5-11 days after the last dose of ciprofloxacin.
- Improvement: Most, but not all, pre-therapy signs and symptoms had subsided in a reasonable period of time but without complete resolution at the follow-up visit 5-11 days after the first/last dose of fosfomycin or 5-11 days after the last dose of ciprofloxacin.
- Failure: This was defined as no apparent response to therapy. This included persistence of all pre-therapy signs and symptoms at the follow-up visit 5-11 days after the first/last dose of fosfomycin and 5-11 days after the last dose of ciprofloxacin.
- Not Assessable: A clinical judgment of cure improvement, or failure could not be made due to various reasons, i.e. improper dose or length of therapy, concomitant antimicrobial

therapy, no pathogen isolated, therapy discontinued due to adverse events, inadequate colony count, susceptibility test not done, or lack of follow-up cultures. The investigator was required to state the circumstances which caused the case to be rated as not assessable.

The primary efficacy outcomes were the difference between fosfomycin and ciprofloxacin in the percentage of responders and bacteriological cure at the follow-up visit 5-11 days after the last dose of antibiotic.

Secondary efficacy variables included in the study were:

- Superinfection - This was defined as the growth of >105 CFU/mL of urine of a pathogen other than the pre-primary pathogen during the course of active therapy. By definition, this outcome could only occur for patients in the ciprofloxacin group as the fosfomycin group was treated with only a single dose of therapy. Thus, for ciprofloxacin-treated patients, if during Study Days 1-6. A pathogen not found at the pre-primary visit at a level >105 CFU/mL was found at a level >105 CFU/mL, the patient was considered to have a superinfection.
- Recurrence - A patient was considered to have a recurrent infection if the following criteria were satisfied:
  - 1. A pre-primary culture was taken within the appropriate time window.
  - 2. The patient has had a documented bacteriological cure at primary evaluation.
  - 3. One or more of the cultures evaluated at the post-primary visit after documentation of a cure showed that the original pathogen, which was at a level >10^5 CFU/mL at baseline.
- New Infection - A patient was considered to have a new infection if the following criteria were satisfied:
  - A culture was taken at the primary or post-primary visit (defined below)
  - A pathogen, other than the species found at baseline at a >105 CFU/mL of urine, was present at a level >10^5 CFU/mL of urine

Definitions of pre-primary, primary and post-primary were different for the two drugs given different dosing schedules and pharmacokinetics.

Table 8: Window of days for bacteriological and clinical evaluations, Study MON-US-01

	TIME WINDOW (Days)	
Evaluation	FT	CIPRO
Pre-Primary (Used for superinfection)[a]	N/A	1-6
Pre-Primary (Used for new infection)	1-4	7-10
Primary (Used for primary efficacy evaluations and determination of new infection)	5-11	11-17
Post-Primary (Used for the determination of recurrence and new infection)	≥12	≥ 18

[a] Superinfection was not a possible outcome for patients in the FT group

Patients without a positive urine culture collected within 48 hours of enrolment were considered a screening failure and were not evaluable for efficacy analysis in either the intention-to-treat (ITT) or evaluable populations. They were either removed from the study or completed the protocol-described treatment course according to investigator discretion and were also included in the safety analyses.

Antimicrobial susceptibility testing was performed for uropathogens cultured at baseline using the in vitro disc diffusion methods in the site-identified laboratories of the investigator, further

details of these were not provided. Disc diameter susceptibility requirements were >16 mm for fosfomycin and >21 mm for ciprofloxacin.

Empty blister packs were viewed at the end of the study and any residual tablets were counted.

6.2.1.5. Randomisation and blinding methods

A predetermined randomisation list was prepared separately for each centre by the sponsor (how this was done is not listed). Allocation numbers provided centrally by the sponsor were written on each patient's case report form. Treatments were coded by the sponsor and the randomisation code was not revealed to study subjects, observers, study monitors or data reviewers. In a medical emergency, investigators could request the blind be broken ?how often done.

Patients received identically appearing placebo tablets for 7 days (fosfomycin arm) or a placebo sachet at commencement of therapy (ciprofloxacin arm).

6.2.1.6. Analysis populations

- **Safety population**. All randomised patients who received at least one dose of study medication were included in the safety analyses. All patients had a midstream urine culture performed at study entry but if this did not culture >105 CFU/mL urine of at least one uropathogen, they were considered a screening failure and either continued or discontinued therapy, at the discretion of the investigator. They were removed from the efficacy analysis but included in the safety analysis.
- **Intention-to-treat analysis**. All randomised patients with a baseline MSU culture of >105 CFU/mL urine of at least one uropathogen were included in the intention-to-treat (ITT) efficacy analysis.
- **Evaluable population for efficacy analyses**. The evaluable population for the efficacy analyses was comprised of those ITT patients who, in the opinion of the medical monitor, had uncomplicated UTI, for whom the initially susceptible, UTI-defining uropathogen was susceptible to both fosfomycin and ciprofloxacin, and who were considered compliant ie had taken at least 10 of 14 study medication tablets.

6.2.1.7. Sample size

In the original protocol, the number of patients with pre-treatment cultures required for the clinical study was determined based on a criterion that would ensure adequate statistical power to detect a clinically relevant reduction in cure rates after fosfomycin treatment relative to an expected ciprofloxacin cure rate. The sample size computation assumed a ciprofloxacin cure rate of 90%, a fosfomycin cure rate of 80% and a one-tailed 0.05 level of significance. The initial sample size computation required 155 evaluable patients per group to provide 80% power to detect a statistically significant difference between ciprofloxacin and fosfomycin bacteriological cure rates. The protocol was amended on February 10, 1992 to increase the sample size to 220 evaluable patients per group due to a change from a one-tailed to a two-tailed 0.05 level of significance. A total of 877 patients were enrolled into the study in an effort to ensure that 220 evaluable patients in each treatment group would complete the study.

6.2.1.8. Statistical methods

The treatment groups were compared with respect to baseline demographic variables. Quantitative variables, such as age, were analyzed using a t-est while qualitative variables, such as race, were analyzed using a Chi-square contingency table analysis or Fisher's exact test.

The treatment groups were compared with respect to categorical efficacy outcomes, such as bacteriological and clinical outcome, using a Fisher's exact test. For the primary outcomes, the 95% one-sided confidence interval for the difference between the treatment groups was determined using a Normal approximation to the Binomial distribution. When analyzing the

primary efficacy variables, no center-adjusted analysis was performed. This approach was, in part, adopted because approximately two-thirds of the centers had fewer than ten patients in one or both of the treatment groups. In addition, the usual significance testing associated with the logistic regression model would be suspect because of the high response rates.

Regarding symptom scores, the treatment groups were compared at baseline using a t-test.

At each post-baseline visit the treatment groups were compared with respect to the change from baseline using a t-test. For each treatment group the significance of the mean change from baseline was determined using a paired t-test. All other quantitative efficacy variables were analyzed using a test to make drug group comparisons while qualitative variables were analyzed using a Fisher's exact t-test.

Statistical significance was declared if the two-sided p-value was 0.05.

6.2.1.9. Participant flow

In the study, 877 patients were enrolled with 432 (49%) randomised to receive fosfomycin and 445 (51%) randomised to receive ciprofloxacin. 149/432 (34%) of the fosfomycin patients and 180/445 (40%) of the ciprofloxacin group were screening failures, most commonly because urine culture did not confirm UTI at baseline. 231/283 (82%) of the fosfomycin intention-to-treat patients completed therapy and were evaluable for efficacy. 212/265 (80%) of the ciprofloxacin ITT patients completed therapy and were evaluable for efficacy. 52 /283 (18%) of fosfomycin ITT patients and 53/265 (20%) of ciprofloxacin patients were not evaluable for efficacy. The most common reasons for not being evaluable were lack of susceptibility to both drugs (37 who received fosfomycin, 41 who received ciprofloxacin), protocol violation (7 fosfomycin, 3 ciprofloxacin), and non-compliance defined as less than 10 tablets taken (8 fosfomycin, 9 ciprofloxacin).

The study was terminated as planned when sufficient patients had accrued for the statistical analysis.

Table 9: Schedule of follow-up visits, Study MON-US-01

Visit	Study Day	Study Timepoint
1	0	First Day of Therapy (Prior to dosing)
1A[a]	2 - 4	48-96 hrs after first dose
2	5 - 9[b]	5-9 days after first dose
3	11 - 15[c]	5-9 days after last dose
4	---	4-6 weeks after last dose

[a] Optional clinic visit; all patients were either to be seen in clinic or contacted via telephone.
[b] For FT patients, the visit scheduled for Days 5-9 was the Primary Evaluation Visit.
[c] For CIPRO patients, the visit scheduled for Days 11-15 was the Primary Evaluation Visit.

6.2.1.10. Major protocol violations/deviations

A small number (9 fosfomycin patients and 5 ciprofloxacin patients) were precluded from efficacy analysis due to protocol deviations. Reasons for protocol violation are listed and included predisposing factors for UTI, administration of antispasmodics, alternative diagnosis, prolonged symptoms, and too many UTIs within the last 12 months.

6.2.1.11. Baseline data

- **Demographics**. With respect to patient race and age, the two groups were statistically similar. In both groups, the majority of patients were Caucasian (87% and 89% in the fosfomycin and ciprofloxacin groups, respectively). The median age at study start was 32

years (range: 18-90 years) in the fosfomycin group and 33 years (range: 18-82 years) in the ciprofloxacin group. Almost half the patients in each treatment group were in the 18-30 year age group. Patient groups were of similar height and weight and there were no significant differences between the groups in number of days symptomatic, numbers of UTIs in the previous 12 months or previous urogenital surgery. Similarly, for both the intention to treat (ITT) and evaluable populations, there were no significant demographic differences between ciprofloxacin and fosfomycin groups in age, race, height, weight, numbers of UTIs in the past 12 months or previous urogenital surgery.

- **Clinical and bacteriological assessments**. Among all patients enrolled, 58% (252/432) of fosfomycin patients and 60% (269/445) of ciprofloxacin patients were evaluated bacteriologically at Day 18 or later. Clinical assessments were performed for 59% (256/432) of fosfomycin patients and 61% (273/445) of ciprofloxacin patients through Day 18 or later. The large reduction in patient numbers through the course of the study primarily reflect screening failures who were mostly discontinued from the study. Most of these were in patients with urinary symptoms but whose urinary cultures at baseline did not confirm UTI. The mean time to final visit was 25.8 days for fosfomycin patients and 26.9 days for ciprofloxacin patients (p=0.31).
- **Compliance with medication**. Ciprofloxacin / placebo tablets were to be administered twice daily for 7 days (14 total doses). Patients assigned to the fosfomycin group took an average of 12.6 placebo tablets over the average course of therapy which lasted 5.5 days. Patients assigned to the ciprofloxacin therapy took an average of 12.7 ciprofloxacin tablets over an average of 5.6 days. Patients who took 10 or more ciprofloxacin / placebo tablets were considered to be compliant. This was 363/432 (84%) of fosfomycin and 383/445 (86%) of ciprofloxacin patients. There were no statistically significant differences in either the duration of therapy or number of doses administered between the two treatment groups.

  Baseline antimicrobial susceptibility. In the ITT population, 87% (246/283) of fosfomycin patients and 85% (224/265) of ciprofloxacin patients, baseline urinary pathogens were found to be susceptible to both fosfomycin and to ciprofloxacin. The difference was neither statistically (p= 0.46) nor clinically significant. For all of 548 ITT patients in both treatment groups, 543 baseline urinary isolates were tested for susceptibility to fosfomycin and 529 isolates were tested for susceptibility to ciprofloxacin. The majority of isolates tested were E coli. Of those, 99% (444/450) were found to be susceptible to fosfomycin and 99% (430/436) were found to be susceptible to ciprofloxacin. In isolates of S saprophyticus. the second most common organism isolated, susceptibility to fosfomycin was 45% (9/20), whereas 95% (21/22) of S saprophyticus isolates were susceptible to ciprofloxacin. Overall, 94% (509/543) of isolates tested were sensitive to fosfomycin and 97% (508/529) of isolates tested were sensitive to ciprofloxacin. Results for the primary efficacy outcome
- **Patient disposition.** The 283 fosfomycin patients and 265 ciprofloxacin patients who were not screening failures were evaluated as the intention to treat (ITT) population. Of those. 82% (231/283) of the fosfomycin patients and 80% (212/265) of the ciprofloxacin patients were deemed evaluable for efficacy analysis and identified as the evaluable population. The evaluable subpopulation was comprised of those ITT patients who, in the opinion of the medical monitor, had uncomplicated UTI, for whom the initially susceptible, UTI-defining uropathogen was susceptible to both fosfomycin and ciprofloxacin, and who had also taken at least 10 of 14 study medication tablets.
- **Exclusions**. Of the 105 ITT patients who were excluded from the evaluable population, 37/52 fosfomycin and 41/53 ciprofloxacin group patients had pathogens that were not susceptible to both study drugs. Ten ITT patients (seven fosfomycin, three ciprofloxacin) were excluded prior to breaking the blind, for baseline deviations of protocol entrance requirements. Finally, 17 lTT patients (eight fosfomycin, nine ciprofloxacin) were excluded

from the evaluable population because they were not compliant with study medication. There was no statistically significant between-group difference in the number of patients considered evaluable for efficacy analysis (p=0.67).

- **Concomitant antimicrobial therapy.** Of all patients enrolled, 25% of fosfomycin patients (108/432) and 13% of ciprofloxacin patients (59/445) took an antibiotic medication during the course of the study (p<0.01). This significant difference remained in both the ITT and evaluable populations. In the ITT population, 28% of fosfomycin patients (79/283) and 14% of ciprofloxacin patients (37/265) took an antibiotic medication during the study (p<0.01). In the evaluable population, 26% of the fosfomycin patients (61/231) and 14 % of ciprofloxacin patients (29/212) took an antibiotic medication during the study (p<0.0I).

Comment: This is the major design flaw of this study. Patients taking concomitant antibiotics are considered discontinuations and excluded from the efficacy analysis for both the ITT and evaluable populations. These patients are highly likely to have taken concomitant antibiotics due to treatment failure. These patients should have been included in ITT and evaluable populations for the efficacy analysis. Note that for both the ITT and evaluable populations, significantly more fosfomycin patients took concomitant antibiotics, compared to fosfomycin. This suggests that fosfomycin had inferior efficacy but this was not analysed properly due to the study design flaw.

- **Discontinuations.** Among ITT patients, 31% (88/283) of fosfomycin patients and 16% (43/265) of ciprofloxacin patients discontinued from the study at or before Visit 4 (p<0.01). Among evaluable patients. 28% (65/231) of fosfomycin patients and 13% (28/212) of ciprofloxacin patients discontinued at or before Visit 4 (p<0.01). The difference is largely due to the greater percentage of treatment failures occurring with fosfomycin (15% for both ITT and evaluable populations) than with ciprofloxacin (3% for ITT, 2% for evaluable populations). Treatment failure was also the most common reason for discontinuation for the fosfomycin patients in both populations.

- **Bacteriological efficacy.** The bacteriological cure rates in the ITT population were 83% (225/270) of fosfomycin patients and 99% (231/233) of ciprofloxacin patients. The ninety-five percent one-sided confidence interval for the upper bound on the difference in the cure rates was 19.7%. Seventeen percent (45/270) of fosfomycin patients and 1% (2/233) of ciprofloxacin patients in the ITT population were determined to have a bacteriological failure of therapy (p<0.01). Among evaluable patients, 84% (189/224) of fosfomycin patients and 99% (187/188) of ciprofloxacin patients were determined to have a bacteriological cure. The ninety-five percent one-sided confidence interval for the upper bound on the difference in the cure rates was 19.2%. Sixteen percent (35/224) of fosfomycin patients and 1 % (1/188) of ciprofloxacin patients in the evaluable population were determined to have a bacteriological failure of therapy (p<0.01).

  The bacteriological cure rate for the ITT population by baseline uropathogen was determined. Following fosfomycin therapy, 87% (201/232) of patients with *E. coli* infections, 77% (10/13) with *Klebsiella pneumoniae* infections and 56% (5/9) with *Staphylococcus saprophyticus* infections were classified as cured. Following ciprofloxacin therapy, 99% (194/196) of patients with *E coli* infections and 100% of patients with *S saphrophyticus* and (12/12) and *K pneumoniae* (616) infections were cured. Susceptibility testing on *S. saprophyticus* showed three of the four isolates tested out of nine isolates available from fosfomycin-treated patients were resistant to fosfomycin, while only one of the 13 tested out of 14 total isolates in the ciprofloxacin-treated patients was resistant to ciprofloxacin.

  The most prevalent pathogen in the evaluable patients was *E coli*. In the fosfomycin patients, there was a total of 204 patients with an infection caused by *E coli* of which 87% (177/204) were classified as a bacteriological cure. Among the 171 ciprofloxacin-treated patients in

whom *E coli* was isolated, the bacteriological cure rate was 99% (170/171). There were fewer than ten evaluable patients with any one other pathogen in either treatment group.

- **Clinical efficacy.** In the ITT population, 81 % (207/256) of patients in the fosfomycin group and 94% (217/230) of patients in the ciprofloxacin group were considered to have had a clinical cure (p<0.01). The ninety-five percent one-sided confidence interval for the difference in the cure rates was 18.2%. Sixteen percent (40/256) of the fosfomycin patients and 6% (13/230) of the ciprofloxacin patients showed clinical improvement but were not considered cured. Four percent (9/256) of the fosfomycin patients failed when evaluated clinically; none of the ciprofloxacin patients failed. Eighty-three percent (177/214) of the fosfomycin patients and 95% (178/188) of the ciprofloxacin patients were classified as having a clinical cure (p<0.01). The ninety-five percent one-sided confidence interval for the difference in the cure rates was 17.0%. Seventeen percent (37/214) of fosfomycin patients and 5% (10/188) of ciprofloxacin patients were deemed clinical failures.

  Of the 283 patients treated with fosfomycin in the ITT population, 221 patients had an *E. coli* infection. Of those, 81 % (179/221) were classified as post-therapy clinical cures. Eighty-three percent of patients (10/12) with *K. pneumoniae* infection and 75% (6/8) patients with *S. saprophyticus* infection were considered to have a clinical cure. Among ciprofloxacin patients, clinical cure rates were 94% (184/196) for *E. coli,* 100% (6/6) for *K. pneumoniae,* and 100% (10/10) for *S. saprophyticus*.

  Among fosfomycin patients in the evaluable population, clinical cure rates were 83% (163/196) for *E. coli,* 100% (7/7) for *K. pneumoniae,* and 75% (3/4) for *S. saprophyticus* infections. In evaluable ciprofloxacin patients, the clinical cure rate for *E. coli* was 95% (162/171) and was 100% for both *K. pneumonie* (3/3) and S. *saprophyticus* (6/6).

6.2.1.12. Results for other efficacy outcomes

- **Superinfection**. This was not assessable for fosfomycin as only one dose of active drug was given. There was no superinfection in 100/100 (100%) of ciprofloxacin patients who were assessed for this secondary efficacy measure.
- **Recurrence**. Eighty-six percent (183/213) of fosfomycin patients and 96% (210/218) of ciprofloxacin patients had no recurrence (p<0.01). Of the 30 fosfomycin patients with recurrence, seven patients had an E.coli infection that was found to be of a different biotype than that originally isolated at baseline. Of the eight ciprofloxacin patients with recurrence, three patients were found to have a different E. coli strain post-therapy than pre-therapy.
- **New infections.** Ninety-one percent (255/280) of fosfomycin patients and 96% (249/259) of ciprofloxacin patients had no new infections (p=0.02).

6.2.1.13. Bacteriological outcome at final visit

The results from the bacteriological assessments made post-baseline were examined in terms of success or failure-type outcomes. A patient was considered a success if infecting baseline organisms (>105 CFU/ml) were reduced to levels of <104 CFU/ml and the patient had <104 CFU/ml at the time of the final visit. Patients with failure-type outcomes (presence of uropathogen at >105 CFU/ml at final visit) included patients who developed superinfection, recurrence and/or new infection during the study. Patients with failure-type final outcomes also included patients for whom the original infecting pathogen persisted throughout the study (to final bacteriological assessment).

In the ITT population, 80% (199/250) of fosfomycin patients and 95% (225/238) of ciprofloxacin patients were considered successes, with failure-type outcomes occurring in 20% (51/250) of fosfomycin patients and 5% (13/238) of ciprofloxacin patients (p<0.01). Similar results were seen in the evaluable population. Seventy-nine percent (155/196) of fosfomycin patients and 96% (175/185) of ciprofloxacin patients were successes, with 21% (41/196) of

fosfomycin patients and 5% (10/185) of ciprofloxacin patients having failure-type outcomes (p<0.01).

6.2.1.14. Evaluator commentary, Study MON-US-01

Study design

- This study complies with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice and in my opinion is a pivotal study. It appears well-designed in accord with accepted guidelines for both products in the early 1990s. There is a major issue with the evaluable and ITT populations excluding treatment failures related to discontinuations from concomitant antibiotic use which will be discussed further below.
- Centres from the list of study sites appear to be a mix of family medical centres, hospital outpatient clinics and emergency rooms. It is presumed that they were predominantly or all outpatients though this is not explicitly mentioned. The patient population and objectives are for the same indication as requested in Australia.
- The ciprofloxacin dose of 250 mg bd is adequate for the treatment of lower UTI (Grayson ML 2010) and is an appropriate comparator, although for several reasons (resistance development, cost, adverse events) fluoroquinolones like ciprofloxacin would not be first line therapy for uncomplicated UTIs then or now in Australia. Nevertheless, one would expect a high efficacy rate of 95% or greater if ciprofloxacin were to be used. Dose selection of fosfomycin also appears reasonable. Inclusion and exclusion criteria were also reasonable.
- The sponsor states that the placebo sachet and tablets were matched for appearance but not whether they were matched for taste. It would be important to know this as Monurol usually has a mandarin or orange juice flavour plus sweetener.
- The method of preparation of the predetermined randomisation list held centrally by the sponsor is not listed. There is no mention of the assessment of the success of blinding or whether there was any deliberate or inadvertent breaking of the blind. There is also no mention of whether independent assessors where used to ask about adverse events so presumably this was not done ie it appears that the blinded medical practitioner who enrolled them also asked about adverse events at follow-up visits.
- Although p values are reported for outcome variables, 95% confidence intervals are only reported for bacteriological cure and bacteriological failure rates.
- Length of followup of patients was satisfactory.

Study conduct

- The initial study protocol was followed until the amendments of March 1991. Presumably the main amendment to allow longer duration of symptoms prior to enrolment was due to poor enrolment rates. I think this is reasonable.
- Statistical methods appear reasonable although I am unsure as to why it was necessary to change from a one-tailed to a two-tailed 0.05 level of significance. Recommend that a biostatistician be consulted as to the impact if any of this change to the study. This study had two primary outcomes and used the critical p-value of 0.05 for declaring statistical significance. Although p values were provided for all efficacy outcomes, confidence intervals were rarely provided. Confidence intervals were only provided for bacteriological efficacy.
- The definition of efficacy variables appear reasonable. Bacteriological efficacy definition is fairly standard. Clinical efficacy was appropriately scored by a blinded investigator on a 4-point symptom scale. The definitions of the secondary efficacy variables are satisfactory.

- Presumably as the study was conducted in the USA, most microbiology laboratories used the NCCLS (now CLSI) method of antimicrobial susceptibility testing, although this is not explicitly stated. Resistance and susceptibility testing zone diameter size breakpoints remain the same today for both fosfomycin and ciprofloxacin.
- The most likely reason for the higher concomitant antibiotic usage in the fosfomycin group resulting in discontinuation was clinical and bacteriological failure requiring additional antibiotic treatment.

Study outcomes

- The groups appear to be well-matched at baseline with half the patients in 18-30 year age group and a median age of 32 and 33 years. Eight-eight per cent of the patients were Caucasian. There were a large number of screening failures, predominantly patients with dysuria but without confirmed UTI on urine culture, this is a common clinical issue in young females that many experienced doctors are familiar with, genital and vulval complaints frequently present with dysuria. The high screening failure rate is likely to be consistent with this.
- The study participants appear representative of those who might receive the medicine in usual clinical practice if approved ie female patients with lower UTIs.
- The participant flow appears satisfactory with good completion rates and similar percentages of screening failures and lack of evaluability in both groups. The populations all appear appropriate for the efficacy and safety analyses and there is no apparent bias or lack of generalizability. The main analysis population corresponds to that specified in the study protocol.
- Other cationic drugs apart from antacids were not specified in the exclusion criteria but this is immaterial to the outcomes as ciprofloxacin is superior in efficacy to fosfomycin in this study and other cations might have lowered ciprofloxacin efficacy rates.
- In this study, both fosfomycin and ciprofloxacin have good clinical and bacteriological efficacy with clinical cure rates of 81% for fosfomycin and superior cure at 94% for ciprofloxacin in the ITT populations ($p<0.01$). Bacteriological efficacy was 83% for fosfomycin and 99% for ciprofloxacin in the ITT population ($p<0.01$). Ciprofloxacin was superior to fosfomycin in terms of clinical and bacteriological efficacy and bacteriological outcome at end of study which as well as efficacy considers issues of new infection, superinfection and recurrence. The recurrence rate in the fosfomycin group was 14% and this was significantly higher than in the ciprofloxacin arm (4%). Susceptibility testing results of the recurrent isolates is not reported and would be of some interest. Resistance development after therapy is of critical importance for new antmicrobial groups.
- When efficacy by organism type is considered, the majority of the patients had E coli infection, which was isolated in 85.1% of fosfomycin ITT patients and 84.1% of ciprofloxacin. For E coli, ciprofloxacin was had a bacteriological ITT cure of 99% compared to 87% for fosfomycin. The p value for this result in the study could not be located but it looks statistically significant. In Australia, E coli accounts for 70-95% of acute uncomplicated UTI (Therapeutic Guidelines Antibiotic 2014).
- Numbers of pathogens for any other organisms apart from E coli were too low to allow any statistically meanful comparision of efficacy between fosfomycin and ciprofloxacin. However, the susceptibility of fosfomycin against Staphylococcus saphyrophyticus in this study is of some concern, with only 9/20 isolates (45%) susceptible, compared to 21/22 (95%) susceptible to ciprofloxacin. S. saphrophyticus is the second most common pathogen implicated in uncomplicated UTIs in Australia, accounting for 5-10% of episodes (Therapeutic Guidelines Antibiotic 2014). S. saphrophyticus is most common in sexually active young women, causing “honeymoon cystitis” and in fact is a marker of new onset of

sexual activity. This group of women are at higher risk of pregnancy as they are sexually active and at peak childbearing age. Fosfomycin has variable activity against S saphrophyticus. There would be some concern therefore recommending the use of fosfomycin in pregnancy from the efficacy point of view, given the higher likelihood of S. saphrophyticus and the consequences of untreated infection in a pregnant woman (miscarriage, fever, fetal loss) compared to a UTI in nonpregnant woman.

FDA Comments about the study design

- In the related later study MON-US-03, the FDA has evaluated this study as follows: "In its evaluation of the efficacy of FT in the MON-US-01 and MON-US-02 trials, the FDA presented results to an Advisory Committee based on criteria which differed in certain respects from those defined prospectively in the protocols. Primarily, the FDA included the use of antibiotics for UTI as a criterion for failure and data from patients with "missing" visits were handled either by excluding the patient from the modified ITT analysis (for non-completers who discontinued for reasons other than treatment failure or related reasons) or by assigning outcomes on a case-by-case basis (for non-completers who remained in the modified ITT population because their discontinuation reason was related to treatment failure)".
- It would be of use to ask the Sponsor if they have performed or have access to the following FDA-recommended analyses on the data: "The primary analysis was performed on the modified ITT population. The modified ITT population consists of ITT patients who completed the study or ITT patients who discontinued due to treatment failure or related reasons. Efficacy assessments in the Modified ITT population were adjusted for concomitant antibiotic use for UTI. Outcomes for missing visits were assigned on a case-by-case basis". Please ask the Sponsor to provide this information if it was performed for review at the second round assessment.

Overall statement, Study MON-US-01

- This study is reasonably well-designed and conducted though the concerns of the FDA above are noted. It shows that a single 3g dose of fosfomycin has good clinical and bacteriological efficacy in the treatment of uncomplicated lower UTIs in adult women. Single dose fosfomycin has lower cure rates than 7 days of ciprofloxacin against the predominant pathogen E coli. Fosfomycin's activity against the second most common pathogen Staphylococcus saphrophyticus is variable.
- The significantly higher usage of concomitant antimicrobials in the fosfomycin arm (108/432 or 25% of fosfomycin patients compared to 59/445 or 13% for ciprofloxacin, $p<0.01$) and the study's failure to use concomitant antimicrobial therapy as a criterion for bacteriological failure would suggest that the efficacy rate of fosfomycin is somewhat lower than stated as an absolute value and also as a percentage difference in relation to ciprofloxacin efficacy. It would be worth statistical review of this issue (or obtaining the FDA documents as this may have already been done).

6.2.2. Study ID MON-US-02 (Harnack, 1994)

6.2.2.1. Study design, objectives, locations and dates

This was a phase 3, prospective, parallel, multicentre, double-blind, double-dummy randomised safety and efficacy study of female patients with acute uncomplicated lower UTI. The study has many similarities to Study MON-US-01 including the same study design, the same sponsor, the same monitor and statistical consultant and same time period. The major difference is that the comparator is different; it is trimethoprim/sulfamethoxazole (TMP/SMX) rather than ciprofloxacin. Study sites were also different to study US-MON-01. The study was conducted between January 1991 and April 1993 in 30 centres in the United States. Centres enrolled

between 3 and 78 patients, with 16 study centres enrolling 10 or more patients per treatment group. Each group received one active drug and one placebo.

6.2.2.2. Inclusion and exclusion criteria

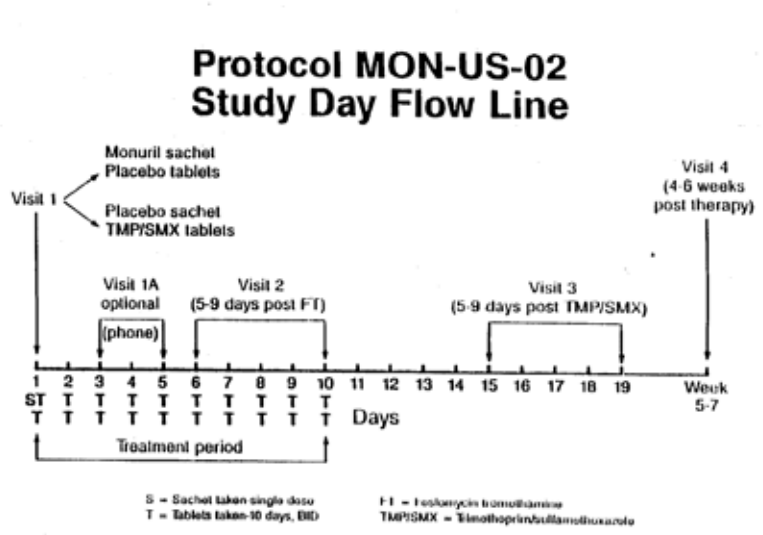
Identical to study US-MON-01; this includes the same 2 amendments made on March 1991.

6.2.2.3. Study treatments

Oral fosfomycin trometamol 3g as a single oral dose was compared to oral TMP/SMX 160 mg/800 mg twice-daily for 10 days. All patients received either a single fosfomycin or placebo sachet at study entry followed by one TMP/SMX or placebo tablet twice daily for 10 days.

The study schematic is shown.

Figure 3: Study schematic of Study MON-US-02



- **Concomitant medication**. Same conditions as study Mon-US-01. No differences between groups of note.

6.2.2.4. Efficacy variables and outcomes

The primary efficacy variables were bacteriological and clinical efficacy.

Bacteriological efficacy was defined as baseline positive midstream urine collection culture (MSU) (defined as $>10^5$ CFU/mL urine of at least one uropathogen) taken within 48 hours of enrolment, followed by levels of the same uropathogen reduced to levels $<10^4$ CFU/mL MSU culture collected at visit 2 for fosfomycin (days 5-11) or visit 3 for TMP/SMX (day 14-20). Note that all patients had cultures collected at visits 2 and 3 as the study was blinded.

Clinical efficacy variables (cure, improvement, failure, not assessable) and the time frames for assessing them were identical to study US-MON-01 with the exception that TMP-SXT is substituted for ciprofloxacin.

Secondary efficacy variables (superinfection, recurrence, new infection) and the time frames for assessing them were identical to study US-MON-01 with the exception that TMP-SXT superinfection was assessed between study day 1-9 due to the longer duration of therapy.

Definitions of pre-primary, primary and post-primary were different for the two drugs given different dosing schedules and pharmacokinetics.

Table 10: Window of days for bacteriological and clinical evaluations, Study MON-US-02

Evaluation	TIME WINDOWS (Days) FT	TMP/SMX
Pre-Primary (Used for superinfection)[a]	N/A	1-9
Pre-Primary (Used for new infection)	1-4	10-13
Primary (Used for primary efficacy evaluations and determination of new infection)	5-11	14-20
Post-Primary (Used for the determination of recurrence and new infection)	≥12	≥ 21

[a] Superinfection was not a possible outcome for patients in the FT group.

Patients without a positive urine culture collected within 48 hours of enrolment were considered a screening failure and were not evaluable for efficacy analysis in either the intention-to-treat (ITT) or evaluable populations. They were either removed from the study or completed the protocol-described treatment course according to investigator discretion and were also included in the safety analyses.

Antimicrobial susceptibility testing was performed for uropathogens cultured at baseline using the in vitro disc diffusion methods in the site-identified laboratories of the investigator, further details of these were not provided. Disc diameter susceptibility requirements were >16 mm for fosfomycin and >16 mm for TMP/SMX.

Empty blister packs were viewed at the end of the study and any residual tablets were counted.

6.2.2.5. Randomisation and blinding methods

Randomisation methods are the same as in study Mon-US-01.

Patients received identically appearing placebo tablets for 10 days (fosfomycin arm) or a placebo sachet at commencement of therapy (TMP/SMX arm).

6.2.2.6. Analysis populations

Definitions of the safety population and the intention-to-treat analysis for efficacy population is the same as in study US-MON-01.

The evaluable population for the efficacy analyses was comprised of those ITT patients who, in the opinion of the medical monitor, had uncomplicated UTI, for whom the initially susceptible, UTI-defining uropathogen was susceptible to both fosfomycin and TMP/SMX, and who were considered compliant ie had taken at least 14 of 20 study medication tablets.

6.2.2.7. Sample size

In the original protocol, the number of patients with pre-treatment cultures required for the clinical study was determined based on a criterion that would ensure adequate statistical power to detect a clinically relevant reduction in cure rates after fosfomycin treatment relative to an expected TMP/SMX cure rate. The sample size computation assumed a TMP/SMX cure rate of 90%, a fosfomycin cure rate of 80% and a one-tailed 0.05 level of significance. The initial sample size computation required 155 evaluable patients per group to provide 80% power to detect a statistically significant difference between ciprofloxacin and fosfomycin bacteriological cure rates. The protocol was amended on February 10, 1992 to increase the sample size to 220 evaluable patients per group due to a change from a one-tailed to a two-tailed 0.05 level of significance. A total of 854 patients were enrolled into the study in an effort to ensure that 220 evaluable patients in each treatment group would complete the study.

6.2.2.8. Statistical methods

The same methods were used as in study MON-US-01.

6.2.2.9. Participant flow

In the study, 854 patients were enrolled with 426 (50%) randomised to receive fosfomycin and 428 (50%) randomised to receive TMP/SXT. 135/426 (32%) of the fosfomycin patients and 162/428 (38%) of the TMP/SXT group were screening failures, most commonly because urine culture did not confirm UTI at baseline. 213/291 (73%) of the fosfomycin intention-to-treat patients completed therapy and were evaluable for efficacy. 193/266 (73%) of the TMP/SXT ITT patients completed therapy and were evaluable for efficacy. 78/291 (27%) of fosfomycin ITT patients and 73/266 (27%) of TMP/SXT patients were not evaluable for efficacy. The most common reasons for not being evaluable were lack of susceptibility to both drugs (57who received fosfomycin, 51 who received TMP/SXT), protocol violation (7 fosfomycin, 8 TMP/SXT), and non-compliance defined as less than 14 tablets taken (12 fosfomycin, 14 TMP/SXT).

The study was terminated as planned when sufficient patients had accrued for the statistical analysis.

Table 11: Schedule of follow-up visits, Study MON-US-02

TABLE 3.1: Schedule of Follow-up Visits (STUDY MON-US-02)

Visits	Study Day	Study Timepoint
1	0	First Day of Therapy (Prior to dosing)
1A[a]	2 - 4	48-96 hrs after first dose
2	5 - 9[b]	5-9 days after first dose
3	14-18[c]	5-9 days after last dose
4	—	4-6 weeks after last dose

[a] Optional clinic visit, all patients were either to be seen in clinic or contacted via telephone.
[b] For FT patients, the visit scheduled for Days 5-9 was the Primary Evaluation Visit.
[c] For TMP/SMX patients, the visit scheduled for Days 14-18 was the Primary Evaluation Visit.

6.2.2.10. Major protocol violations/deviations

A small number (12 fosfomycin patients and 10 TMP/SMX patients) were precluded from efficacy analysis due to protocol deviations. Reasons for protocol violation are listed and include drug hypersensitivity, more than 3 UTIs in the past year and prolonged duration of UTI symptoms.

6.2.2.11. Baseline data

- **Demographics**. With respect to patient race and age, the two groups were statistically similar. In both groups, the majority of patients were Caucasian (85% and 86% in the fosfomycin and TMP/SMX groups, respectively). The median age at study start was 32 years (range: 18-88 years) in the fosfomycin group and 31.5 years (range: 18-90 years) in the TMP/SMX group. Almost half the patients in each treatment group were in the 18-30 year age group. Patient groups were of similar height and weight and there were no significant differences between the groups in number of days symptomatic, numbers of UTIs in the previous 12 months or previous urogenital surgery. Similarly, for both the intention to treat (ITT) and evaluable populations, there were no significant demographic differences between TMP/SMX and fosfomycin groups in age, height, weight, numbers of UTIs in the past 12 months or previous urogenital surgery. With respect to patient race, the two ITT treatment groups were statistically different (p=0.03). The largest difference was in blacks (fosfomycin =11%. TMP/SMX = 8%). In both groups, the majority of patients were Caucasian (84% and 86% in the fosfomycin and TMP/SMX groups, respectively). Similarly,

the two evaluable treatment groups were statistically different with respect to race (p=0.02). The largest differences were in Caucasians (fosfomycin=83%, TMP/SMX=88%) and blacks (fosfomycin=11%,, TMP/SMX=6%). However, once again majority of patients in each treatment group were Caucasian. This difference between treatment groups in race at baseline is unlikely to be clinically significant.

- **Clinical and bacteriological assessments**. Among all patients enrolled, 60% (255/426) of fosfomycin patients and 58% (247/428) of TMP/SMX patients were evaluated bacteriologically at Day 21 or later. Clinical assessments were performed for 60% (256/426) of fosfomycin patients and 59% (251/428) of TMP/SMX patients through day 21 or later. The large reduction in patient numbers through the course of the study primarily reflect screening failures who were mostly discontinued from the study. Most of these were in patients with urinary symptoms but whose urinary cultures at baseline did not confirm UTI. For all enrolled patients the mean time to final visit was 28.2 days for fosfomycin patients and 27.0 days for TMP/SMX patients (p=0.32).
- **Compliance with medication.** TMP/SMX placebo tablets were to be administered twice daily for ten days (20 total doses). Patients assigned to the fosfomycin group took an average of 17.2 placebo tablets over the average course of therapy which lasted 8.0 days. Patients assigned to the TMP/SMX therapy took an average of 16.3 TMP/SMX tablets over an average of 7.5 days, the difference in doses was statistically significant (p=0.01). This is unlikely to be clinically significant.
- **Baseline antimicrobial susceptibility.** In the ITT population, 80% (234/291) of fosfomycin patients and 81% (215/266) of TMP/SMX patients, baseline urinary pathogens were found to be susceptible to both fosfomycin and to TMP/SMX. The difference was neither clinically or statistically significant (p=0/92). For all of 557 ITT patients in both treatment groups, 546 baseline urinary isolates were tested for susceptibility to fosfomycin and 536 isolates were tested for susceptibility to TMP/SMX. The majority of isolates tested were *E coli*. Of those, 98% (454/464) were found to be susceptible to fosfomycin and 89% (406/455) were found to be susceptible to TMP/SMX. For the second most common isolate, *Proteus mirabilis,* susceptibility to fosfomycin was 71% (15/21) and TMP/SMX, it was 100% (20/20). In isolates of *S saprophyticus,* the third most common organism isolated, susceptibility to fosfomycin was 56% (9/16), whereas 100% (16/16) of *S saprophyticus* isolates were susceptible to TMP/SMX. Overall, 93% (510/546) of isolates tested were sensitive to fosfomycin and 90% (482/536) of isolates tested were sensitive to TMP/SMX.

6.2.2.12. Results for the primary efficacy outcome

- **Patient disposition.** This is shown in Figure 20. The 291 fosfomycin patients and 266 TMP/SMX patients who were not screening failures were evaluated as the intention to treat (ITT) population. Of those, 73% (213/291) of the fosfomycin patients and 73% (193/266) of the TMP/SMX patients were deemed evaluable for efficacy analysis and identified as the evaluable population. The evaluable subpopulation was comprised of those ITT patients who, in the opinion of the medical monitor, had uncomplicated UTI, for whom the initially susceptible, UTI-defining uropathogen was susceptible to both fosfomycin and TMP/SMX, and who had also taken at least 14 of 20 study medication tablets.
- **Exclusions.** Of the 151 ITT patients who were excluded from the evaluable population, 57/78 fosfomycin and 51/73 TMP/SMX patients had pathogens that were not susceptible to both study drugs. Seventeen ITT patients (9 fosfomycin, 8 TMP/SMX) were excluded prior to breaking the blind, for baseline deviations of protocol entrance requirements. Finally, 17 lTT patients (12 fosfomycin, 14 TMP/SMX) were excluded from the evaluable population because they were not compliant with study medication. There was no statistically significant between-group difference in the number of patients considered evaluable for efficacy analysis (p=0.87).

- **Concomitant antimicrobial therapy.** Of all patients enrolled, 23% of fosfomycin patients (99/426) and 19% of TMP/SMX patients (83/428) took an antibiotic medication during the course of the study (p=0.18).
- **Discontinuations.** Among ITT patients, 24% (72/291) of fosfomycin patients and 20% (53/266) of TMP/SMX patients discontinued from the study at or before Visit 4 (p 0.22). Among evaluable patients, 20% (43/213) of fosfomycin patients and 7% (14/193) of TMP/SMX patients discontinued at or before Visit 4 (p<0.01). The difference is largely due to the greater percentage of treatment failures occurring with fosfomycin (13% for ITT, 12% for evaluable populations) than with TMP/SMX (5% for ITT, 2% for evaluable populations). Treatment failure was also the most common reason for discontinuation for the fosfomycin patients in both populations.
- **Bacteriological efficacy.** The bacteriological cure rates in the ITT population were 89% (246/276) of fosfomycin patients and 98% (207/211) of TMP/SMX patients. The ninety-five percent one-sided confidence interval for the upper bound on the difference in the cure rates was 12.4%. Eleven percent (30/276) of fosfomycin patients and 2% (4/211) of TMP/SMX patients in the ITT population were determined to have a bacteriological failure of therapy (p<0.01). Among evaluable patients, 90% (187/208) of fosfomycin patients and 98% (166/169) of TMP/SMX patients were determined to have a bacteriological cure. The ninety-five percent one-sided confidence interval for the upper bound on the difference in the cure rates was 12.2%. Ten percent (21/208) of fosfomycin patients and 2% (3/169) of TMP/SMX patients in the evaluable population were determined to have a bacteriological failure of therapy (p<0.01).

  The bacteriological cure rate for the ITT population by baseline uropathogen was determined. Following fosfomycin therapy, 90% (211/234) of patients with *E coli* infections, 100% (13/13) with *Proteus mirabilis* infections, 70% (7/10) with *Klebsiella pneumoniae* infections, and 75% (3/4) with *Staphylococcus saprophyticus* infections were classified as having been cured.

  Following TMP/SMX therapy, 98% (183/187) of ITT patients with *E coli* infections and 100% with *P. mirabilis* (7/7), S. *saprophyticus* (6/6) and *K pneumoniae* (5/5) infections were cured.

  Susceptibility testing on *S. saprophyticus* showed two of the five isolates tested out of six isolates available from fosfomycin-treated patients were resistant to fosfomycin, while none of the 11 total isolates tested in the TMP/SMX-treated patients was resistant to TMP/SMX.

  The most prevalent pathogen in the evaluable patients was *E coli.* In the fosfomycin patients, there was a total of 182 patients with an infection caused by *E coli* of which 90% (163/182) were classified as a bacteriological cure. Among the 159 TMP/SMX-treated patients in whom *E coli* was isolated, the bacteriological cure rate was 98% (156/159). There were fewer than ten evaluable patients with any one other pathogen in either treatment group
- **Clinical efficacy.** In the ITT population, 77 % (205/265) of patients in the fosfomycin group and 93% (195/209) of patients in the TMP/SMX group were considered to have had a clinical cure (p<0.01). The ninety-five percent one-sided confidence interval for the difference in the cure rates was 21.0%. Twenty-two percent (57/265) of the fosfomycin patients and 7% (14/209) of the TMP/SMX patients showed clinical improvement but were not considered cured. One percent (3/265) of the fosfomycin patients failed when evaluated clinically; none of the TMP/SMX patients failed. In the evaluable population, 76% (156/204) of the fosfomycin patients and 93% (158/169) of the TMP/SMX patients were classified as having a clinical cure (p<0.01). The ninety-five percent one-sided confidence interval for the difference in the cure rates was 22.0%. Twenty-four percent (48/204) of fosfomycin patients and 7% (11/169) of TMP/SMX patients were deemed clinical failures.

Of the 291 patients treated with fosfomycin in the ITT population, 226 patients had an *E coli* infection. Of those, 79% (179/226) were classified as post-therapy clinical cures. Fifty percent (6/12) of the patients with *P. mirabilis* infection, 56% (5/9) of the patients with *K pneumoniae* infection and 75% (3/4) of the patients with S *saprophyticus* infectionwere considered to have a clinical cure. Among TMP/SMX patients, clinical cure rates were 92% (169/184) for *E coli,* 100% (7/7) for *P. mirabilis,* 100% (5/5) for *K pneumoniae,* and 100% (6/6) for S. *saprophyticus.*

Among fosfomycin patients in the evaluable population, clinical cure rates were 77% (138/180) for *E. coli,* 56% (5/9) for *P. mirabilis,* 50% (3/6) for *K. pneumoniae*, and 67% (2/3) for *S. saprophyticus* infections. In evaluable TMP/SMX patients, the clinical cure rate for *E. coli* was 93% (146/157) and was 100% for *K. pneumoniae* (3/3*), P mirabilis* (3/3) and *S. saprophyticus (*3/3).

6.2.2.13. Results for other efficacy outcomes

- **Superinfection.** This was not assessable for fosfomycin as only one dose of active drug was given. There was only one superinfection in the TMP/SMX group.
- **Recurrence.** Eighty-nine percent (209/234) of fosfomycin patients and 94% (190/202) of TMP/SMX patients had no recurrence (p=0.09). Of the 25 fosfomycin patients with recurrence, four patients had an *E. coli* infection that was found to be of a different biotype than that originally isolated at baseline. Of the 12 TMP/SMX patients with recurrence, three patients were found to have a different E. coli strain post-therapy than pre-therapy.
- **New infections.** Ninety-three percent (267/287) of fosfomycin patients and 95% (233/246) of TMP/SMX patients had no new infections (p=0.47).

6.2.2.14. Bacteriological outcome at final visit

- The results from the bacteriological assessments made post-baseline were examined in terms of success or failure-type outcomes. A patient was considered a success if infecting baseline organisms (>10^5 CFU/ml) were reduced to levels of <10^4 CFU/ml and the patient had <10^4 CFU/ml at the time of the final visit. Patients with failure-type outcomes (presence of uropathogen at >10^5 CFU/ml at final visit) included patients who developed superinfection, recurrence and/or new infection during the study. Patients with failure-type final outcomes also included patients for whom the original infecting pathogen persisted throughout the study (to final bacteriological assessment).
- In the ITT population, 86% (222/257) of fosfomycin patients and 91 % (206/226) of TMP/SMX patients were considered successes, with failure-type outcomes occurring in 14% (35/257) of FT patients and 9% (20/226) of TMP/SMX patients (p=0.12). In the evaluable population, 86% (159/1 84) of fosfomycin patients and 90% (160/177) of TMP/SMX patients were successes, with 14% (25/184) of fosfomycin patients and 10% (17/177) of TMP/SMX patients having failure-type outcomes (p=0.26).

6.2.2.15. Evaluator commentary

- This pivotal study has many similarities to Study MON-US-01 including the same study design, the same sponsor (Forest Laboratories), the same monitor and statistical consultant and was conducted in the same population and same time period in the early 1990s in the United States. The major difference is that the comparator for fosfomycin is TMP/SMX rather than ciprofloxacin.

Study design

- All the comments about study design for study US-MON-01 apply to study US-MON-02. These include my comments on compliance with Guidance on Good Clinical practice,

location of study sites, taste of placebo sachet, fosfomycin dose, independence of assessors, scarcity of reporting 95% confidence intervals and length of followup.

- In study MON-US-02, unlike Study MON-US-01, there was no difference in incidence of concomitant antimicrobial therapy between fosfomycin and TMP/SMX groups.

Study outcomes

- The groups appear to be well-matched at baseline with half the patients in 18-30 year age group and a median age in each group of 32 and 31.5 years. There were minor differences in race between the two groups but 85% of the patients were Caucasian. In my opinion, the racial differences are not clinically significant. As for Study US-MON-01, there were a large number of screening failures.
- The participant flow appears satisfactory with good completion rates and similar percentages of screening failures and lack of evaluability in both groups. The populations all appear appropriate for the efficacy and safety analyses and there is no apparent bias or lack of generalizability. The main analysis population corresponds to that specified in the study protocol.
- In this study, both fosfomycin and TMP/SMX have good clinical and bacteriological efficacy with clinical ITT cure rates of 77% for fosfomycin and superior cure at 93% for TMP/SMX in the ITT populations ($p<0.01$). Bacteriological efficacy was 89% for fosfomycin and 98% for TMP/SMX in the ITT population ($p<0.01$). Thus, TMP/SMX was superior to fosfomycin in terms of clinical and bacteriological efficacy. For bacteriological outcome in ITT patients at end of study (which as well as efficacy takes into consideration issues of new infection, superinfection and recurrence), 86% of fosfomycin patients and 91%of TMP/SMX patients were successful, but this was not statistically significant ($p =0.12$). It should be noted that a large number of ITT patients (57/291 or 19.5% for fosfomycin and 64/266 or 24% for TMP/SMX) did not have urine cultures performed for recurrence. Of those that did have urine cultures for recurrence, there was no statistically significant difference in recurrence between the two groups (89% fosfomycin and 94% of TMP/SMX patients had no recurrence, $p=0.09$). Susceptibility testing results of the recurrent isolates is not reported and would be of some interest. Resistance development after therapy is of critical importance for new antimicrobial groups.
- When efficacy by organism type is considered, the majority of the patients had E coli infection, which was isolated in 421/487 (86%) of ITT patients. For E coli, TMP/SMX had a bacteriological cure rate in the ITT population of 98% compared to 90% for fosfomycin. The P value for the E coli bacteriological cure rate is not listed. In Australia, E coli accounts for 70-95% of acute uncomplicated UTI (Therapeutic Guidelines Antibiotic 2014).
- Numbers of pathogens for any other organisms apart from E coli were too low to allow any statistically meanful comparison of efficacy between fosfomycin and TMP/SMX. There were very few patients with S saphrophyticus, a uropathogen which can have variable susceptibility to fosfomycin. For this organism, three out of four ITT patients treated with fosfomycin and all six patients treated with TMP/SXT had bacteriological cure.
- The FDA's comments about study design referred to in the evaluator commentary for study US-MON-01 also apply here, particularly the failure to include concomitant antimicrobial usage as a criterion for failure. As differences in concomitant antimicrobial therapy between the two treatment groups were not significant (99/426 or 23% for fosfomycin, 83/428 or 19% for TMP/SMX, $p=0.18$), this is less important than for study US-MON-02.

Overall statement, Study MON-US-02

- This study is well-designed and conducted. It shows that a single 3g dose of fosfomycin has good clinical and bacteriological efficacy in the treatment of uncomplicated lower UTIs in

adult women. Efficacy rates are significantly lower than the comparator TMP/SMX but are acceptable.

6.2.3. Study MON-US-03 (Bowman 1996)

6.2.3.1. Study design, objectives, locations and dates

This was a phase 3, prospective, parallel, multicentre, double-blind, double-dummy randomised safety and efficacy study of female patients with acute uncomplicated lower UTI. The study has many similarities to Studies MON-US-01 and US-MON-02 including the same study design, same study analysis plan and the same sponsor (Forest Laboratories). The statistical consultant is different and the study is conducted approximately 2 years later than study MON-US-01 and study US-MON-02. Study sites are different to the two earlier studies. The protocols are very similar but the major difference is that the comparator is different; it is nitrofurantoin. The study was conducted between March 1993 and October 1994 in 26 centres in the United States. Centres enrolled between 1 and 80 patients, with 10 study centres enrolling 15 or more patients per treatment group.

6.2.3.2. Inclusion and exclusion criteria

Inclusion criteria were identical to the final amended version of US-MON-01 and US-MON-02 with 96 hours of symptoms allowed. The single difference to the earlier studies is that the age limit was lowered, patients 12 years or older could be enrolled.

Exclusion criteria were very similar to US-MON-01 and US-MON-02. The major difference was that patients with creatinine clearance of less than 60 mls per minute were excluded (a lower creatinine clearance of <30 mls per minutes was used as an exclusion for US-MON-01 and US-MON-02).

There were 2 amendments during the study in Jan-Feb 1993. These specifically the dosing schedule in relation to food for the purposes of clarity and also allowed methods of birth control, see below:

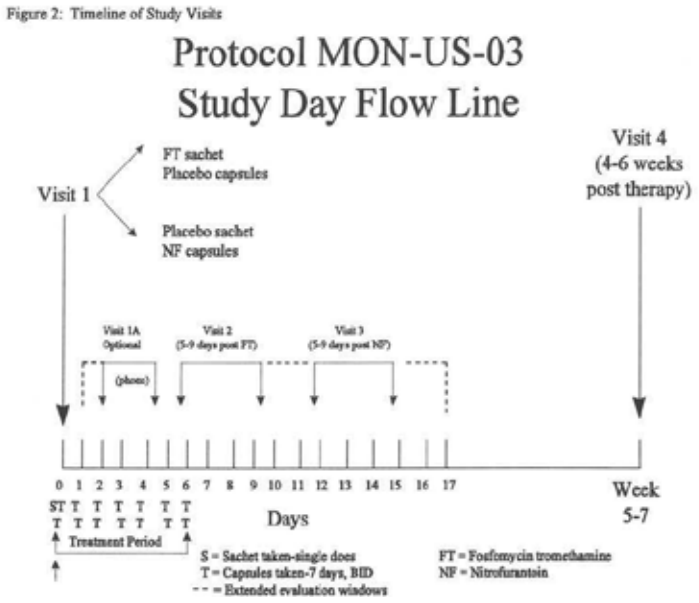
- Patients were to be treated for seven days. On Day l, all patients were to take one sachet dissolved in 3 - 4 oz of water in the morning. The sachet was to be given after at least two hours of fasting. On Day l, at least two hours after the sachet was taken, all patients were to take one capsule in the morning with food. On Day l, the second capsule was to be taken in the evening with food. On Days 2 through 7, patients were to take one capsule each morning and one capsule each evening with food.
- All females between the ages of 12 and 18 who were not sexually active and had a negative pre-therapy pregnancy test could use absolute abstinence as a method of birth control. Females of childbearing potential 18 years of age or older must have used a medically accepted effective method of birth control.

6.2.3.3. Study treatments

Oral fosfomycin trometamol 3g as a single oral dose was compared to oral nitrofurantoin monohydrate/macrocrystals 100 mg twice-daily for 7 days. All patients received either a single fosfomycin or placebo sachet at study entry followed by one placebo or nitrofurantoin or capsule twice daily for 7 days. Each group received one active drug and one placebo.

The study schematic is shown in Figure 4, below:

Figure 4: Study schematic of study MON-US-03



Concomitant medication: Same conditions as study Mon-US-01. No differences between groups of note.

6.2.3.4. Efficacy variables and outcomes

The primary efficacy variable was a combination of bacteriological and clinical efficacy and was assessed by evaluation of:

- Bacteriological response (cure or failure);
- UTI symptomatology based on the absence of all (cure) or the presence of one or more (failure) of six UTI symptoms; and investigator assignment of cure, improvement or failure; and
- Overall clinical responses (considering together the bacteriological response and absence or presence of UTI symptomatology).

Table below shows the window of days for bacteriological and clinical evaluations.

Table 12: Window of days for bacteriological and clinical evaluation, Study US-MON-03

[redacted] Window of Days for Bacteriological and Clinical Evaluations (STUDY MON-US-03)

	TIME WINDOWS (Days)	
Evaluation	FT	NF
Pre-Primary (Used for superinfection)[a]	N/A	1-6
Pre-Primary (Used for new infection)	1-4	7-10
Primary (Used for primary efficacy evaluations and determination of new infection)	5-11	11-17
Post-Primary (Used for the determination of recurrence and new infection)	≥ 12	≥ 18

[a] Superinfection was not a possible outcome for patients in the FT group.

Bacteriological response was the primary efficacy parameter. Primary bacteriological evaluation windows were Days 5 to 11 for fosfomycin and Days 11 to 17 for nitrofurantoin. Four assessments of bacteriological response were made in three temporal windows. The assessments made were: Day 5-11 (Visit 2), Day 11-17 (Visit 3), Final Visit after Day 17 (with

respect to original uropathogen only and also taking into consideration not only the original uropathogen but also the incidence of new infection and recurrence).

UTI symptomatology and clinical response was assessed at Visit 2, Visit 3 and Final Visit.

Susceptibility tests to both drugs were performed by local (site specific) laboratories for all pathogens cultured in numbers > 10^5 CFU/mL at baseline or greater than 10^4 CFU/mL during the study. Isolates with a disc sensitivity zone >16 mm (fosfomycin) or >17 mm (nitrofurantoin) were considered susceptible. Presumably as the study was conducted in the USA, the majority of laboratories used the NCCLS (now CLSI) methodology, these are also the NCCLS disc zone breakpoints. This information was not provided.

Secondary efficacy variables were the incidence of superinfection, recurrence and new infection as well as the time to recurrence and new infections. These definitions were the same as in studies US-MON-01 and US-MON-02.

Patients without a positive urine culture collected within 48 hours of enrolment were considered a screening failure and were not evaluable for efficacy analysis in either the intention-to-treat (ITT) or evaluable populations. They were either removed from the study or completed the protocol-described treatment course according to investigator discretion and were also included in the safety analyses.

Empty blister packs were viewed at the end of the study and any residual tablets were counted.

6.2.3.5. Randomisation and blinding methods

Randomisation methods are the same as in studies Mon-US-01 and US MON-02.

Patients received identically appearing placebo tablets for 7 days (fosfomycin arm) or a placebo sachet at commencement of therapy (nitrofurantoin arm).

6.2.3.6. Analysis populations

Bacteriological cure and failure rates were calculated for the efficacy populations:

- The ITT population: A patient was analyzed in the efficacy analyses of the ITT population if baseline urine culture showed the presence of at least 105 CFU/mL of a known uropathogen.
- The Modified ITT population which was inclusive of all patients who had:
  - >105 CFU/mL of a known uropathogen on baseline culture and
  - who completed the study OR, if they did not complete the study, they discontinued due to treatment failure or failure-related reasons ie. was a treatment failure.

Use of concomitant antimicrobial therapy was considered a treatment failure.

In addition, subset analyses were performed for patients in the Modified ITT population in four age groups, for patients with body weight < 50 kg and >50 kg, and for patients with and without a prior history of recent (within 12 months) UTI. For these subsets, bacteriological outcomes at the primary assessment window were determined.

Each patient in the Modified ITT population was considered to be either a bacteriological 'cure' or 'failure' at each of the windows assessed. Patients without cultures available in the specified windows were assessed on a case-by-case basis. The assignments were presented individually.

Specifically, these analysis populations satisfied the FDA criteria criticisms of earlier related studies US-MON-01 and US-MON-02, ie:

- The primary analysis was performed on the modified ITT population. The modified ITT population consists of ITT patients who completed the study OR ITT patients who discontinued due to treatment failure or related reasons.

- Efficacy assessments in the Modified ITT population were adjusted for concomitant antibiotic use for UTI.
- Outcomes for missing visits were assigned on a case-by-case basis.
- An overall clinical evaluation, combining bacteriological results and clinical symptomatology, was made.

6.2.3.7. Sample size

In the protocol, the number of patients with positive pre-treatment cultures required for the clinical study was determined based on a criterion that would ensure adequate statistical power to detect a clinically relevant difference in cure rates after fosfomycin treatment relative to an expected nitrofurantoin cure rate. The initial sample size computation required 151 evaluable patients per group to provide 80% power to detect a statistically significant difference between nitrofurantoin and fosfomycin bacteriological cure rates. Assuming an 80% observed bacteriological cure rate for both treatments, the sample size computation required 151 evaluable patients per group to generate a 95% confidence interval with width + 9% for the true difference in bacteriological cure rates between treatment groups. A total of 749 patients were enrolled into the study in an effort to ensure that 151 evaluable patients in each treatment group would complete the study.

6.2.3.8. Statistical methods

The treatment groups were compared with respect to baseline demographic variables. Quantitative variables, such as age, were analyzed using a t-test while qualitative variables, such as race, were analyzed using a Chi-square contingency table analysis or Fisher's exact test, as appropriate. The treatment groups were compared with respect to categorical efficacy outcomes, such as bacteriological and clinical outcome, using a Fisher's exact test. For the primary outcomes, the 95% two-sided confidence interval for the difference between the treatment groups was determined using a Normal approximation to the Binomial distribution. When analyzing the primary efficacy variables, no center-adjusted analysis was performed. This approach was, in part, adopted because approximately two-thirds of the centers had fewer than ten patients in one or both of the treatment groups. Regarding symptom scores, the treatment groups were compared at baseline using a t-test. At each post-baseline visit, the treatment groups were compared with respect to the change from baseline using a t-test. For each treatment group, the significance of the mean change from baseline was determined using a paired t-test. All other quantitative efficacy variables were analyzed using a t-test to make drug group comparisons while qualitative variables were analyzed using a Fisher's exact test. Statistical significance was declared if the two-sided p-value was <0.05.

6.2.3.9. Participant flow

In the study, 749 patients were enrolled with 375 (50%) randomised to receive fosfomycin and 374 (50%) randomised to receive nitrofurantoin. 103/375 (27%) of the fosfomycin patients and 113/374 (30%) of the nitrofurantoin group were discontinued as initial urine culture did not confirm UTI. 260/272 (96%) of the fosfomycin intention-to-treat patients either completed therapy or did not complete therapy for treatment-failure related reasons and were considered the modified intention-to-treat group and were evaluable for efficacy. 237/261 (91%) of the nitrofurantoin intention-to-treat patients either completed therapy or did not complete therapy for treatment-failure related reasons and were considered the modified intention-to-treat group and were evaluable for efficacy. Of the 12 fosfomycin and 24 nitrofurantoin patients who were not evaluable for efficacy, the most common reasons were adverse event or intercurrent illness (7 fosfomycin, 16 nitrofurantoin), protocol violation (5 each group), noncompliance (1 fosfomycin, 4 nitrofurantoin).

The study was terminated as planned when sufficient patients had accrued for the statistical analysis.

Table 13: Schedule of follow-up visits, study US-MON-03

[redacted] Schedule of Follow-up Visits (STUDY MON-US-03)

Visits	Study Day	Study Timepoint
1	0	First Day of Therapy (Prior to dosing)
1A[a]	2 - 4	48-96 hrs after first dose
2	5 - 9[b]	5-9 days after first dose
3	11-15[c]	5-9 days after last dose
4	---	4-6 weeks after last dose

[a] Optional clinic visit, all patients were either to be seen in clinic or contacted via telephone.
[b] For FT patients, the visit scheduled for Days 5-9 was the Primary Evaluation Visit.
[c] For NF patients, the visit scheduled for Days 11-15 was the Primary Evaluation Visit.

6.2.3.10. Major protocol violations/deviations

One site which enrolled 25 fosfomycin and 26 nitrofurantoin patients used its own in-house laboratory for urinalyses and urine cultures. Problems in the laboratory were uncovered that made urine culture results from that laboratory questionable. After the problem was discovered, the site continued to enrol but sent cultures to a different laboratory. The Appendices contain a listing of all the analyses excluding that site. Other protocol deviations in the study were considered minor.

6.2.3.11. Baseline data

- **Demographics**. With respect to patient race and age, the two groups were statistically similar. In both groups, the majority of patients were Caucasian (85% and 86% in the fosfomycin and nitrofurantoin groups, respectively). The median age at study start was 27 years (range: 15-92 years) in the fosfomycin group and 27 years (range: 16-80 years) in the nitrofurantoin group. More than half the patients in each treatment group were in the 12-30 year age group. Patient groups were of similar height and weight and there were no significant differences between the groups in number of days symptomatic, and numbers of UTIs in the previous 12 months. Similarly, for the modified intention to treat (ITT) population, there were no significant demographic differences between nitrofurantoin and fosfomycin groups in age, race, or numbers of UTIs in the past 12 months. Fosfomycin patients had a median height of 64 inches compared to 65 inches for nitrofurantoin (p=0.02) but there were no significant differences in weight. This is not likely to be clinically significant. In both groups, the majority of patients were Caucasian (85% and 86% in the fosfomycin and nitrofurantoin groups, respectively).
- **Compliance with medication**. Nitrofurantoin/placebo capsules were to be administered twice daily for seven days (14 total doses) with no significant differences between the two groups. Patients assigned to the fosfomycin group took an average of 12.9 placebo capsules over the average course of therapy which lasted 6.8 days. Patients assigned to the nitrofurantoin therapy took an average of 12.8 nitrofurantoin capsules over an average of 6.8 days. A patient was considered to have been compliant with the treatment regimen if she ingested the fosfomycin/placebo sachet in water and if she took 10 or more of 14 protocol-

required nitrofurantoin/placebo capsules. Among all patients, 86% (323/375) of fosfomycin patients and 85% (318/374) of nitrofurantoin patients were compliant with the treatment regimen (p=0.73). Capsule return rate was the same between the two groups with an average return rate of 1.1 capsules for both groups.

- **Baseline antimicrobial susceptibility**. In the modified ITT population, 79% (206/260) of fosfomycin patients and 76% (180/237) of nitrofurantoin patients were found to be susceptible to both drugs at baseline (p=0.838). For all of the 497 Modified ITT patients in both treatment groups, 495 baseline urinary isolates were tested for susceptibility to fosfomycin and 484 isolates were tested for susceptibility to nitrofurantoin. The majority of isolates tested were E. coli. Of those, 99% (397/401) were found to be susceptible to fosfomycin (i.e., disk zone diameters were >16 mm) and 91% (357/392) were found to be susceptible to nitrofurantoin (zone size >17 mm). For the second most common isolate, Klebsiella pneumoniae, susceptibility to fosfomycin was 75% (18/24) and to nitrofurantoin it was 52% (12/23). In isolates of Proteus mirabilis, the third most common organism cultured, susceptibility to fosfomycin was 92% (22/24); whereas, 4% (1/24) Proteus mirabilis isolates were susceptible to nitrofurantoin. Isolates of Staphylococcus saprophyticus, the fourth most common organism cultured, were 54% (13/24) susceptible to fosfomycin and 96% (23/24) susceptible to nitrofurantoin. Overall, 94% (466/495) of isolates tested were sensitive to fosfomycin and 84% (405/484) of isolates tested were sensitive to nitrofurantoin.

6.2.3.12. Results for the primary efficacy outcome

Patient disposition. This is shown below. Patients in the modified Intent-to-Treat (modified ITT) population (N=497) were evaluated for efficacy. There were no siginificant differences between the two modified ITT groups for time in study or concomitant antimicrobial usage.

Table 14: Patient numbers by treatment group for each population, Study MON-US-03

Analysis Group (Population Identifier)	FT N (% of Pop.)	NF N (% of Pop.)	TOTAL N (% of Pop.)
Patients Randomized, Enrolled and Treated, Valid for Safety Analysis (ALL)	375 (50)	374 (50)	749 (100)
Patients without evidence of at least 10^5 CFU/mL of a known uropathogen at baseline (Not Evaluated in ITT or Modified ITT analyses)	103 (48)	113 (52)	216 (100)
ITT Population (Presented in ATTACHMENT III)	272 (51)	261 (49)	533 (100)
Patients Excluded from the Modified ITT Population (Presented in ATT\CHMENT I)	12 (33)	24 (67)	36 (100)
Patients in the Modified Intent-to-Treat Group (Modified ITT)	260 (52)	237 (48)	497 (100)

% of Pop. = Percentage of Population
N = Number of patients
Note that two ITT patients who completed the trial but did not have bacteriological data in the After Day 17 window were excluded from the modified ITT population.
Cross-Reference: Raw Data Listing 1.

- **Exclusions.** A total of 36 ITT patients (12 fosfomycin; 24 nitrofurantoin) were excluded from the modified ITT population. The ITT patients who were excluded were those who discontinued from the study for reasons other than treatment failure or treatment failure-related reasons. These are individually listed and appear reasonable.
- **Concomitant antimicrobial therapy.** Of all patients enrolled, 21% of fosfomycin patients (80/375) and 25% of nitrofurantoin patients (92/374) took an antibiotic medication or

phenazopyridine or pyridium for UTI during the course of the study (p=0.298). In the Modified ITT population, 25% of fosfomycin patients (65/260) and 30% of nitrofurantoin patients (72/237) took an antibiotic medication or phenazopyridine or pyridium for UTI during the study (p=0.192). Appropriately, and unlike the earlier related studies MON-US-01 and MON-US-02, patients who took these were considered treatment failures.

- **Discontinuations.** The most common reason listed for discontinuation of all enrolled patients from both the fosfomycin and nitrofurantoin treatment groups was screening failure, most commonly baseline urine culture which did not confirm UTI. Screening failure was listed as at least one of the reasons for discontinuation from the study for 92 fosfomycin patients (25% (92/375) of all fosfomycin patients] and for 112 nitrofurantoin patients (30% (112/374) of all NF patients]. Among fosfomycin modified ITT patients, treatment failure required the discontinuation of 12% (32/260) of the population. Eight percent (18/237) of modified ITT nitrofurantoin patients were excluded from the study due to treatment failure. Discontinuations and the reasons for them are individually listed in Attachment II and these appear reasonable. Patients who were discontinued from the study due to adverse event or intercurrent illness are presented in detail in the safety section.
- **Bacteriological efficacy.** Among patients in the Modified ITT population, there were no significant differences in bacteriological cure rates at Visit 2, Visit 3 or the Final Visit. Eighty-three per cent (215/260) of fosfomycin patients and 88% (209/237) of nitrofurantoin patients were determined to have a bacteriological cure within the Study Day 5-11 Window (visit 2) (p=0.099) By evaluation in the Day 11-17 Window (Visit 3), bacteriological cure rates were 77% and 76% for both for the fosfomycin and nitrofurantoin groups respectively (p=0.752). After Day 17 (Final Visit), evaluations again showed comparable cure rates of 70% and 65% (p=0.338) for fosfomycin and nitrofurantoin patients, respectively.
- The bacteriological cure rate by baseline uropathogen was determined for the modified ITT population. Following fosfomycin therapy, 86% (188/220) of patients with *E. coli* infections, 73% (8/11) with *Klebsiella pneumoniae* infections, 69% (9/13) with *Staphylococcus saprophyticus* infections and 60% (6/10) with *Proteus mirabilis* infection were classified as having been cured. Following nitrofurantoin therapy, 78% (145/186) of patients with *E. coli* infections, 77% (10/13) with *K. pneumoniae* infections, 83% (10/12) *S. saprophyticus* infections, and 43% (6/14) *P. mirabilis* infections were classified as having been cured.
- **Overall clinical evaluation**. Clinical symptomatology evaluations in the Modified ITT population showed no statistically significant differences between treatment groups in symptom resolution. There were no statistically significant differences in clinical cure rates in the Modified ITT population at Days 5-11, Days 11-17, after Day 17 and at Final Visit. Sixty-five percent (169/260) of the patients in the fosfomycin group and 68% (162/237) of the patients in the nitrofurantoin group were considered a cure (p=0.45) at Days 5-11. At Days 11-17, 70% (182/260) of the patients in the FT group and 70% (166/237) of the patients in the nitrofurantoin group were considered a cure (p=1.00). After Day 17,67% (173/260) of the patients in the fosfomycin group and 63% (149/237) of the patients in the nitrofurantoin group were considered a cure (p=0.40), and at Final Visit, 62% (162/260) of the patients in the fosfomycin group and 60% (142/237) of the patients in the nitrofurantoin group were considered a cure(p=0.65).

6.2.3.13. Results for other efficacy outcomes, modified ITT patients

- **Superinfection**. This was not assessable for fosfomycin as only one dose of active drug was given. There were only two superinfections in the nitrofurantoin group.
- **Recurrence.** Eighty-four percent (180/260) of fosfomycin patients and 86% (153/237) of nitrofurantoin patients had no recurrence (p=0.676). Did recurrent isolates develop resistance to study drug? Unlike MON-US-01 and MON-US-02, there is some data on susceptibility testing results and resistance development after treatment in MON-US-03.

This is a "list of patients with bacteriologcal and symptomatology evaluations assigned by the sponsor" and contains individual data for 34 patients. However, 35 fosfomycin patients and 26 nitrofurantoin patients had recurrence proven by culture so this data set is not complete.

- **New infections.** Ninety-two percent (239/260) of fosfomycin patients and 94% (218/237) of nitrofurantoin patients had no new infections (p=0.374).

6.2.3.14. Bacteriological outcome at final visit

For the determination of bacteriological outcome at the Final Visit, the results from all bacteriological assessments made post-baseline were examined. A patient was considered a cure if infecting baseline organisms (> 10^5 CFU/mL) were reduced to levels of <10^4 CFU/mL and the patient had less than 10^4 CFU/mL for all uropathogens at the time of the last visit. Patients with failure outcomes included patients who developed superinfection, recurrence and/or new infection during the study and patients who required additional antibiotic therapy for UTI.

In the Modified ITT population, 65% (170/260) of fosfomycin patients and 62% (147/237) of nitrofurantoin patients were considered cures, with failures occurring in 35% (90/260) of fosfomycin patients and 38% (90/237) of nitrofurantoin patients (p=0.456).

6.2.3.15. Efficacy subset analyses

Bacteriological outcome at primary visit by age

To determine if patient age at baseline impacted bacteriological outcome, patients were divided into four age groups and data sets were compared. The age groups analyzed were: 12-30 years, 31-50 years, 51-65 years, and greater than 65 years. Patients in the two treatment groups were similarly distributed in age strata. Patients in each age group had bacteriological response rates that were quite similar to those seen in the population as a whole. For each age group there was no statistical difference in the cure rates between the two treatment groups.

Clinical symptomatology evaluation by visit by age

Clinical symptomatology outcome was also assessed for patients in each of four age groups in three evaluation periods. For all age groups, at the Day 5-11 and after Day 17 windows, cure rates for clinical symptomatology were statistically similar between treatment groups. In the Day 11-17 window, for patients aged 51-65 years, a statistical difference (p=0.004) between groups was noted with 21% (3/14) of fosfomycin patients and 77% (13/17) of nitrofurantoin patients being cured. Noting the small sample size, this finding is not considered to be clinically important.

Bacteriological evaluation at the primary assessment window and clinical symptomatology by visit by body weight

Within treatment group comparisons of the bacteriological responses of those patients weighing <50 kg versus those weighing >50 kg showed the response rates to be similar within both the fosfomycin and nitrofurantoin treatment groups. Between treatment group comparisons showed fosfomycin and nitrofurantoin bacteriological cure rates to be comparable for patients weighing < 50 kg. For patients weighing >50 kg, the fosfomycin bacteriological cure rate was 82% compared to the nitrofurantoin bacteriological cure rate of 74% (p=0.054).

Bacteriological evaluation at primary visit in patients with and without a previous history of UTI

There were no significant differences in cure between the two treatment groups in patients with and without a history of UTI.

6.2.3.16. Evaluator commentary

- This pivotal study has many similarities to Studies MON-US-01 and US-MON-02 including the same study design and the same sponsor (Forest Laboratories). It has a different comparator antibiotic, nitrofurantoin. It was conducted in 1993-4, two years after Studies MON-US-01 and US-MON-02 and the efficacy analysis variables are handled somewhat differently to the earlier studies, perhaps in response to FDA criticism of Studies MON-US-01 and US-MON-02.

Study design

- All the comments about study design for study US-MON-01 apply to study US-MON-03. These include my comments on compliance with Guidance on Good Clinical practice), location of study sites, taste of placebo sachet, fosfomycin dose, independence of assessors, scarcity of reporting of 95% confidence intervals and length of followup. Teenage females (12- 17 years) were included in this study although they were excluded in the earlier two studies.
- Enrolled patients who had a urine culture confirming UTI at baseline were the ITT population. Those ITT patients who either completed therapy or discontinued therapy for failure-related reasons were the modified ITT population and were evaluable for efficacy variables. This is an improvement in study design and efficacy analysis over Studies MON-US-01 and US-MON-02.
- There was no difference between the two treatment groups in concomitant antimicrobial usage.
- The nitrofurantoin dose of 100 mg bd for 7 days is adequate for the treatment of lower UTI and is an appropriate comparator. The expected efficacy rate of 80% for nitrofurantoin for the sample calculations appears correct.

Study conduct

- The study conduct was similar to studies US-MON-01 and US-MON-02. Sufficient details of outcomes for missing visits is provided.

Study outcomes

- The groups appear to be well-matched at baseline with a predominantly Caucasian population. More than half the patients are in the 12-30 year age group and the median age in both groups is 27 years.
- The participant flow appears satisfactory with good completion and compliance rates and similar percentages of screening failures in both groups. The populations all appear appropriate for the efficacy and safety analyses and there is no apparent bias or lack of generalizability. The main analysis population corresponds to that specified in the study protocol.
- Bacteriological cure rates at the primary assessment visit 5-11 days after completion of therapy) were 83% for fosfomycin and 88% for nitrofurantoin (p=0.099).
- When efficacy by organism type is considered, the majority of the patients had *E coli* infection, which was isolated in 406/497 (82%) of modified ITT patients. For *E coli,* nitrofurantoin had a bacteriological cure rate in the modified ITT population of 78% compared to 86% for fosfomycin. The P value for the E coli bacteriological cure rate is not listed.
- Numbers of pathogens for any other organisms apart from *E coli* were too low to allow any statistically meanful comparison of efficacy between fosfomycin and nitrofurantoin. There were very few patients with *S saphrophyticus*, a uropathogen which can have variable

susceptibility to fosfomycin. For this organism, 9/13 modified ITT patients treated with fosfomycin and 10/12 patients treated with nitrofurantoin had bacteriological cure.

- There is limited data in the data set on resistance development to study drug in bacteriological failures, recurrences or new infections. Is the Sponsor able to provide further information on this (see clinical questions efficacy question 3)?
- Lastly, this study has been published in abbreviated form (Stein 1999).

Overall statement, Study MON-US-03

This study is well-designed and conducted. It shows that a single 3g dose of fosfomycin has good efficacy in the treatment of uncomplicated lower UTIs in teenage and adult women. There were no statistically significant differences in efficacy rates to the comparator nitrofurantoin.

6.3. Other efficacy studies for Indication 1

6.3.1. Nonpivotal randomized, controlled, double-blind, double-dummy treatment studies

Six small double-blind randomised efficacy and safety studies were conducted in Europe in the late 1980s and early 1990s prior to the three key pivotal studies discussed in the previous section. Five are listed in the dossier and one (Selvaggi 1990) is listed in "Literature References" but is reviewed here. These 6 studies predated the GCP which were not yet in force at the time.

The six studies had many similar features. All included adult females with acute uncomplicated UTI and excluded patients with structural abnormalities, renal impairment, and frequent (usually defined as 3-4 per year) or chronic UTIs. The fosfomycin trometamol (Monurol) dose in all 6 studies was a single 3g oral sachet and the comparator antibiotics were fluoroquinolones (3 studies) and one study each for trimethoprim, nitrofurantoin and amoxycillin. All studies required a baseline culture confirming UTI. As discussed, dysuria can be a presentation of other diseases apart from UTI and as a result there were many dropouts in the studies due to negative baseline culture. Most studies excluded from the efficacy analysis patients with culture resistant at baseline to both fosfomycin and the comparator antibiotic, but this was relatively uncommon. These patients were included in the safety analyses.

6.3.1.1. Study Boerema et al 1988 (norfloxacin comparator)

This was a randomised double-blind double-dummy multicentre general practice study conducted in Holland of adult females 16-50 years old with acute symptomatic lower UTI and no structural urinary tract abnormalities. Sixty-one patients received 3g oral fosfomycin as a single dose and 50 patients received norfloxacin 400 mg bd for 7 days. Mean age was 30 in both groups. *E coli* cultured in 80% of fosfomycin patients and 75% of norfloxacin patients. Bacteriological cure rates immediately post therapy (day 7-9) were 90% for fosfomycin and 98% for norfloxacin. At the last visit (day 42), bacteriological cure rates were 62% for fosfomycin and 65% for norfloxacin (p=0.70).

Comment: Small study showing fosfomycin probably equivalent or slightly inferior cure rate to norfloxacin. Patient numbers for bacteriological cure rate immediately post-therapy do not add up and the p value is not correct.

6.3.1.2. Study Richaud 1989 (pefloxacin comparator)

This was a randomised double-blind double-dummy multicentre general practice study conducted in France of adult females aged 18-80 years with acute lower UTI and no structural urinary tract abnormalities. 29 evaluable patients received 3g oral fosfomycin as a single dose and 28 patients received the fluoroquinolone pefloxacin 800 mg as a single oral dose. Mean age was substantially older than the previously discussed studies and was 57.2 years in the fosfomycin group and 51.4 years in the pefloxacin group. *E coli* cultured in 68% of patients.

Bacteriological cure rates at day 8-10 were 26/29 for fosfomycin and 26/28 for pefloxacin (p=0.669). At day 28-35, bacteriological cure rates were 25/29 for fosfomycin and 24/27 for pefloxacin (p=0.583).

Comment: Small study using single dose of a fluoroquinolone which is not an accepted therapy for UTI nowadays, study of historical interest only and for fosfomycin safety data.

6.3.1.3. Study Asscher et al 1991 (trimethoprim comparator)

This randomised double-blind double-dummy study was conducted in Wales of females aged 16-65 years with acute lower UTI and no structural urinary tract abnormalities. Treatment regimens were 3g oral fosfomycin as a single dose compared to200 mg trimethoprim as a single oral dose. Mean age was 39 years. Bacteriological cure rates at day 7 were 25/32 (78%) for fosfomycin and 22/36 (61%) for trimethoprim (p=0.13). At day 42, bacteriological cure rates were 24/32 (75%) for fosfomycin and 20/36 (56%) for trimethoprim (p=0.17). Of the 69 patients analysed for efficacy, 3 in the fosfomycin group and 9 in the trimethoprim group did not complete the study. Of these, one fosfomycin-treated patient and six trimethoprim-treated patients withdrew because of treatment failure (p=0.08).

Comment: Fosfomycin has good efficacy. Trimethoprim efficacy lower than fosfomycin although not statistically significant difference due to small size of study. Trimethoprim now not dosed as a single dose, minimum dosage now of 300 mg and dosed for 3 days ie trimethoprim dose in this study was too low.

6.3.1.4. Study Boerema and Groeneveld 1987 (amoxicillin comparator)

This randomised double-blind double-dummy general practice study of females aged 18-65 years with acute lower UTI and no structural urinary tract abnormalities was conducted in Holland. Treatment regimens were 3g oral fosfomycin as a single dose compared to 3g amoxycillin as a single oral dose. Mean age was 40.6 years (fosfomycin) and 40.9 years (amoxycillin). *E coli* was the pathogen for 79.4% of patients. Bacteriological cure rates at day 2-4 were 12/13 (92%) for fosfomycin and 6/14 (43%) for amoxycillin (p<0.05). At day 3-7, bacteriological cure rates were 15/16 (94%) for fosfomycin and 6/14 (43%) for amoxycillin (p<0.01). At the final visit (day12-36), bacteriological cure rates were 10/14 (72%) for fosfomycin and 4/12 (33%) for amoxicillin (p<0.05).

Comment: Fosfomycin has good efficacy. Amoxicillin is a statistically inferior therapy despite the small numbers in the study. Amoxicillin has not been recommended as first-line therapy of UTIs in Australia for a number of years as beta-lactamase producing strains of *E coli* are common.

6.3.1.5. Study Van Pienbrook et al, 1993 (nitrofurantoin comparator)

This study is included in the dossier. Not all trial data is available but due to the large size of the study it is worthy of discussion. It is a randomised double-blind double-dummy general practice study of females aged 18 years and older with acute lower UTI and no structural urinary tract abnormalities and was conducted in Holland. Treatment regimens were 3g oral fosfomycin as a single dose compared to nitrofurantoin 50 mg qid for 7 days. Mean age was 40.7 years (fosfomycin) and 45.3 years (nitrofurantoin). Bacterial pathogens were not reported in the publication. Clinical efficacy at day 9 was 97/102 (95%) for fosfomycin and 103/109 (94%) for nitrofurantoin. Clinical efficacy at day 42 was 75/91 (82%) for fosfomycin and 75/94 (80%) for nitrofurantoin. Bacteriological efficacy at day 9 is reported as 90% for fosfomycin and 81% for nitrofurantoin. Bacteriological efficacy at day 42 is reported as 93% for fosfomycin and 87% for nitrofurantoin. For bacteriological efficacy, no p-values are provided. The relapse/reinfection rate at day 42 was 5/89 (6%) for fosfomycin and 10/90 (11%) for nitrofurantoin (p=0.24).

Comment: Full study data is not available but the study appears large and well-conducted. Single dose fosfomycin is efficacious and probably equivalent or slightly more efficacious than nitrofurantoin 50 mg qid for 7 days. Nitrofurantoin is now dosed at

100 mg bd but the total daily dose is unchanged so this study is comparable to modern-day dosing of the drug.

6.3.1.6. Study Selvaggi, 1988 (norfloxacin comparator)

This study which is included in the dossier but is reviewed here as although it is small, it is a well-conducted randomized, controlled, double-blind, double-dummy study. Data presentation is limited to a 3-page publication. It is a randomised double-blind double-dummy general practice study of females aged 16 years and older with acute lower UTI and no structural urinary tract abnormalities and was conducted in Italy. Treatment regimens were 3g oral fosfomycin as a single dose compared to norfloxacin 800 mg oral as a single dose. Median age was 39 years (fosfomycin) and 38 years (norfloxacin). E coli was the causative pathogen in 89% of fosfomycin and 77% of norfloxacin patients. Bacteriological efficacy at day 8 was 21/28 (75%) fosfomycin and 21/25 (84%) for norfloxacin which was not statistically significant.

Comment: Both drugs have good efficacy in a small study. Single dose fluoroquinolone therapy is not a recommended therapy in Australia at the present time for multiple reasons including cost, resistance development, and effect on bowel bacterial flora.

6.3.2. Other controlled and uncontrolled clinical studies pertinent to the claimed indication

The dossier contains a large number of clinical studies of the treatment of patients with UTI, with 4 controlled studies and 9 uncontrolled studies. All are reviewed individually in this section, as follows.

The studies have some similarities which are best described here. They are all open-label although some are randomised. They are mostly small studies of females with acute uncomplicated UTI though some included males and some included patients with recurrent UTI, urinary catheters or asymptomatic bacteruria (which in the modern era is not usually treated except in pregnancy. They were all conducted in the 1980s mostly in Europe and hence predate GCP.

6.3.2.1. Study Pontonnier, 1988 (norfloxacin comparator)

This is an open randomised general practice study of females aged 16 years and older with acute lower UTI and no structural urinary tract abnormalities and was conducted in France. Treatment regimens were 3g oral fosfomycin as a single dose compared to norfloxacin 400 mg bd for 5 days. Mean age was 37 years (fosfomycin) and 44 years (norfloxacin). *E coli* was the causative pathogen in 74% of patients. Bacteriological efficacy at day 3-4 post treatment was 31/33(94%) for fosfomycin and 26/30 (87%) for norfloxacin ($p>0.05$). Bacteriological efficacy at day 25-30 post treatment was 22/30 (73%) for fosfomycin and 21/27 (78%) for norfloxacin ($p>0.05$).

Comment: Both fosfomycin and 5 days of norfloxacin have good and equivalent efficacy with the provisos that the trial numbers are small and that the study is not blinded.

6.3.2.2. Study Reynaert et al, 1988 (norfloxacin comparator)

This is an open randomised study of females aged 16-75 years with acute lower UTI. Interestingly, patients were recruited from the psychiatric service of a Dutch hospital. Treatment regimens were 3g oral fosfomycin as a single dose compared to norfloxacin 400 mg bd for 3 days. Mean age was 43 years (fosfomycin) and 53 years (norfloxacin ($p=0.04$). *E coli* was the causative pathogen in 88% (fosfomycin) and 75% (norfloxacin) of patients. Bacteriological efficacy at day 5-12 post treatment was 14/16 (88%) for fosfomycin and 14/16 (88%) for norfloxacin ($p=0.592$). Bacteriological efficacy at one month post treatment was 13/16 (82%) for fosfomycin and 9/16 (56%) for norfloxacin ($p=0.252$).

Comment: Both fosfomycin and 3 days of norfloxacin have good and equivalent efficacy with the provisos that the trial numbers are small and that the study is not blinded.

6.3.2.3. Study Jardin et al, 1987 (pipemidic acid comparator)

This is an open randomised multicentre study of females with acute uncomplicated UTI aged 16-75 years conducted in France. Treatment regimens were 3g oral fosfomycin as a single dose compared to pipemidic acid 400 mg bd for 5 days. Mean age was 39.1 years (fosfomycin) and 41.5 years (pipemidic acid). Bacteriological efficacy 5-10 days after the end of therapy was 122/146 (83.5%) for fosfomycin and 130/143 (90.9%) for pipemidic acid (p>0.05). Bacteriological efficacy at one month post treatment was 113/122 (92.6%) for fosfomycin and 114/122 (93.4%) for pipemidic acid (p>0.05).

Comment: Pipemidic acid was one of the earliest quinolone antibiotics and was never commercially available in Australia, to the best of my knowledge. It has also never been approved or licensed in the United Kingdom, USA or Canada. It was superseded by nalidixic acid and later norfloxacin and ciprofloxacin (Kucers). This study is primarily of use for the safety data. Of note also is that the bacteriological efficacy of fosfomycin was good at 83.5% short-term and 92.6% long-term.

6.3.2.4. Study Dejonckheere, 1988 (norfloxacin comparator, post-operative catheter-associated UTIs)

This is an open randomised study of females aged 16-75 years conducted in Holland. Patients were required to have had a gynaecological surgical intervention requiring urinary catheterisation for some days after the surgery. At the time of removal of the catheter, they were enrolled if they had symptoms of dysuria. They were not required to have other symptoms of UTI such as fever. Treatment regimens were given immediately after catheter removal and were 3g oral fosfomycin as a single dose compared to norfloxacin 400 mg bd for 3 days. Patients without confirmed UTI on culture were excluded from the efficacy analysis but included in the safety analysis. Mean age was 50 years (fosfomycin) and 48 years (norfloxacin). *Enterococcus faecalis* and / or *E coli* were the causative pathogens in 23/30 (fosfomycin) and 21/26 (norfloxacin) of patients. Bacteriological efficacy at study day 7 was 28/29 (96%) for fosfomycin and 23/26 (89%) for norfloxacin. Bacteriological efficacy at one month post treatment was 25/27 (93%) for fosfomycin and 19/20 (95%) for norfloxacin.

Comment: P-values were not provided but efficacy looks good for both norfloxacin and fosfomycin and looks equivalent. Patients were specifically asked about dysuria at the time of catheter removal and removal of the catheter itself could cause dysuria. No other symptoms or signs were required. Presumably therefore many of the cohort could have had asymptomatic bacteruria which is no longer usually treated as it often resolves on removal of the catheter. Therefore the study does not have much clinical utility.

6.3.2.5. Study De Caro, 1984 (no comparator arm)

This is a small open-label study of the treatment of acute lower UTI in 7 males and 12 females. A single 3 g dose of fosfomycin was used. Bacteriological efficacy was 18/19 (95%) at day 2 and 13/19 (68%) at day 7. No antimicrobial susceptibility testing results were reported.

Comment: This small early study is of interest as it is one of the few studies of UTIs which included males. In general, UTIs in males are more difficult to treat than females. However, disappointingly, results were not stratified by sex.

6.3.2.6. Study Di Nola, 1984 (no comparator arm)

This open-label dose-finding study was conducted in Italy early in the development of the drug. Fosfomycin was used to treat simple and complicated UTIs in males and females and also used for prophylaxis.

The dosing schedules and bacteriological efficacy for each were:

- Single dose fosfomycin 3g. Bacteriological efficacy at day 30 was 30/31(97%) for simple UTIs and 6/11 (55%) for complicated UTIs.
- Fosfomycin 3 g once-daily for 7-12 days. Bacteriological efficacy at day 30 was 10/10 (100%) for simple UTIs and 1/1 (100%) for complicated UTI.
- Fosfomycin 3 g for 2 doses given 12 hours apart. Bacteriological efficacy at day 30 was 30/31(97%) for simple UTIs and 7/13 (54%) for complicated UTIs.
- Single dose fosfomycin 3 g (elderly institutionalised patients). Bacteriological efficacy at day 30 was 12/15(80%) for simple UTIs and 0/8 (0%) for complicated UTIs.
- Prophylaxis arm, endoscopies (mostly cystoscopies). Bacteriological efficacy at day 30 was 28/30 (93%).

Overall bacteriological efficacy in dosing schedules listed in 1, 2 and 3 above was 97% for simple UTIs but only 56% for complicated UTIs. Disappointingly, results were not stratified by sex. No culture or susceptibility testing results were reported post-therapy.

Comment: This early dose-finding study indicates that a single 3g oral dose has excellent (97%) bacteriological efficacy in the treatment of simple UTIs. Complicated UTIs have poor bacteriological efficacy with either a single 3 g dose (55%) or two 3g doses in 24 hours (54%). Only one patient with complicated UTI received a daily dose of 3g for 7-12 days so whether this might improve efficacy in this group is uncertain.

6.3.2.7. Study Krejci, 1994 (no comparator arm)

This publication is the report from a questionnaire distributed by the drug company Zambon to 259 urologists. Each urologist was sent 10 questionnaires and asked to complete them between June-October 1992. Data was received on 2137 patients aged 12 years and older treated with fosfomycin. Mean age was 40 years and only 12/2137 patients were male. 82% of the patients had acute UTI. 66% of patients had *E coli* infection. Efficacy was judged clinically and was 92%.

Comment: This study is of limited interest. It is not specified whether the urologists were reimbursed for collecting this data and completing the questionnaire. if so, the potential for bias would be great.

6.3.2.8. Study Marini, 1984 (no comparator arm)

This early open-label study includes 24 females, 12 males with UTIs, the vast majority acute uncomplicated UTIs. Most patients were dosed with 3g as a single dose but at investigator discretion two 3g doses could be given. Bacteriological efficacy for one 3g dose was 15/21 (71%) at day 2-3 and 16/21 (76%) at day 7-9. Bacteriological efficacy for two 3g doses was 11/11 (100%) at day 2-3 and also at day 7-9. Efficacy results were not stratified by sex.

Comment: Good efficacy for single dose fosfomycin in acute uncomplicated UTI in an early small open-label study.

6.3.2.9. Study Moroni, 1984 (no comparator arm)

This early open-label study showed good efficacy in acute uncomplicated UTI with bacteriological efficacy 2-4 days after treatment of 43/43 (100%) and 34/36 (94.4%) at 7-10 days after treatment. Most patients received a single 3g dose but some received two 3g doses over 24 hours. The majority of patients with UTI were female

Comment: Good efficacy for single dose fosfomycin in acute uncomplicated UTI in an early small open-label study. Fosfomycin was also given for endoscopic prophylaxis which is not currently recommended.

6.3.2.10. Study Moroni 1987a (no comparator arm)

This was an open-label study of 91 women aged 20-91 years (mean 59 years) treated with a single dose of 3g fosfomycin. Bacteriological efficacy at day 21-28 was 41/51 (80.4%) for uncomplicated lower UTIs, 11/14 (78.6%) for recurrent lower UTIs and 20/25 for asymptomatic bacteruria (76.9%).

Comment: Good efficacy for single dose fosfomycin in acute uncomplicated UTI in an early small open-label study. Asymptomatic bacteruria now no longer usually treated.

6.3.2.11. Study Rizzo 1984 (no comparator arm)

This was an open-label study of 22 women aged 30-85 years treated with fosfomycin. Some patients had symptomatic UTI but some had asymptomatic bacteruria (proportion unclear). Bacteriological efficacy at day 7 was 9/10 (90%) for patients treated with a single 3g dose and 9/12 (75%) for patients treated with two 3g doses within a 24-hour period.

Comment: Good efficacy for single dose fosfomycin in an early small open-label study. Asymptomatic bacteruria now no longer usually treated.

6.3.2.12. Study Rolandi 1984 (dose-finding study, no comparator arm)

This was an open-label study of 23 women and 16 men aged 20-84 years with acute symptomatic UTI. Fosfomycin was dosed either 3g single dose, 3g twice-daily for 2 doses, or 3g daily for 2 doses. Bacteriological efficacy for the single dose arm was 7/9 at day 2-4 and 3/4 at day 7-10. Bacteriological efficacy for the two dose arms were 21/24 at day 2-4 and 23/29 at day 7-10. Results were not stratified by sex.

Comment: Good efficacy for single dose fosfomycin in an early small open-label study. Numbers are small but no obvious advantage to giving two doses of 3g rather than a single 3g dose.

6.3.2.13. Study Group Switzerland 1989 (no comparator arm)

This was an open-label uncontrolled prospective study of 1913 women and 207 men aged 16-75 years with acute uncomplicated symptomatic UTI conducted by 406 Swiss investigators (Monuril Study Group Switzerland). Patients with structural urinary tract abnormalities, more than 4 UTIs in the last 12 months or significant renal impairment were excluded. Fosfomycin was given as a 3g single dose. Mean age was 42 years (females) and 52 years (males). *E coli* was the uropathogen in 78% of cases. Bacteriological efficacy was 1141/1268 (90%) at day 7. Results were not stratified by sex.

Comment: Good efficacy for single dose fosfomycin in a large uncontrolled open-label multicentre study.

6.3.3. Other efficacy studies of importance in "Literature references"

"Literature references" contains a large number of efficacy studies of variable quality. The evaluator has selected the following studies for individual review as they contain important special subpopulations within the proposed indication: UTI in pregnancy (3 studies), elderly patients with UTI (1 study), ESBL-producing E coli UTIs (2 studies) and fosfomycin-resistant UTIs (1 study). Four studies of asymptomatic bacteruria in pregnancy have also been reviewed here for efficacy but are of more importance in the safety analysis.

6.3.3.1. Krcmery et al, 2001 (treatment of UTI in pregnancy, comparator ceftibuten)

This was an open-label randomised prospective study conducted in Slovakia of the treatment of acute symptomatic uncomplicated lower UTI in pregnancy. Patients were randomised to receive either 3g oral fosfomycin single dose or ceftibuten 400 mg orally once-daily for 3 days. Bacteriological efficacy at 28-42 day follow-up was 20/21 (95.2%) for fosfomycin and 18/20 (90%) for amoxicillin-clavulanate (p NS).

Comment: Fosfomycin and ceftibuten have good efficacy in the treatment of UTIs in pregnancy in a small open-label study. This study is also of interest for the safety analysis in pregnancy.

6.3.3.2. Usta et al, 2011 (treatment of UTI in pregnancy, comparator cefuroxime or amoxicillin-clavulanate)

This was an open-label randomised prospective study conducted in Turkey of the treatment of acute symptomatic uncomplicated lower UTI or symptomatic bacteruria in pregnancy. Patients were randomised to receive either 3g oral fosfomycin single dose, amoxicillin-clavulanate 625 mg bd for 5 days or cefuroxime 500 mg orally bd for 5 days. Thirty patients were in each treatment group. Bacteriological efficacy at week 2 was 82.1% for fosfomycin, 81.5% for amoxicillin-clavulanate and 89.7% for cefuroxime (p NS).

Comment: All 3 drugs have good efficacy in the treatment of either UTIs or asymptomatic bacteruria in pregnancy in a small open-label study. Single dose antimicrobial therapy of asymptomatic bacteriuria in pregnancy is not recommended due to lower efficacy rates compared to multiple-day treatment regimens in the Infectious Diseases of America guidelines for the treatment of asymptomatic bacteriuria in adults (Nicolle LE 2005). This study is also of interest for the safety analysis in pregnancy.

6.3.3.3. Bayrak 2007 (treatment of asymptomatic bacteruria in pregnancy)

This is a randomised open non-blinded prospective study of the treatment of asymptomatic bacteriuria in the 2nd trimester of pregnancy. It was conducted in a university hospital in Turkey in 2004-5. Bacteriuria was defined as two consecutive clean-catch urines with $>10^5$ CFU/ml with the same uropathogen isolated in both. Asymptomatic bacteriuria in pregnancy is associated with worse pregnancy outcomes and higher rates of pyelonephritis compared to patients who do not have bacteriuria. Forty-five patients were randomised to single 3g oral dose of fosfomycin. Forty-five patients were randomised to oral cefuroxime 250 mg bd for 5 days. Mean age of patients was 25.4 for fosfomycin and 25.2 for cefuroxime. Gestational age at treatment was 14-18 for fosfomycin and 14-20 for cefuroxime. E coli was isolated in 41/44 fosfomycin and 38/40 cefuroxime patients. Bacteriological eradication at day 7 after treatment occurred in 93.2% of fosfomycin and 95% of cefuroxime patients (p 0.912).

Comment: Both fosfomycin and cefuroxime had good efficacy in the eradication of asymptomatic bacteriuria in pregnancy in this small study. Single dose antimicrobial therapy of asymptomatic bacteriuria in pregnancy is not recommended due to lower efficacy rates compared to multiple-day treatment regimens in the Infectious Diseases of America guidelines for the treatment of asymptomatic bacteriuria in adults (Nicolle LE 2005). This study is primarily of interest for the safety analysis in pregnancy.

6.3.3.4. De Cecco and Ragni, 1987 (treatment of asymptomatic bacteruria in pregnancy)

This was an open-label randomised prospective study conducted in Italy of the treatment of asymptomatic bacteriuria in pregnancy. Patients at or after the 8th week of pregnancy gestation were randomised to receive 3g oral fosfomycin single dose or pipemidic acid (an early fluoroquinolone) 200 mg bd for 7 days. Bacteriological efficacy at 4 week follow-up was 50/52 (96%) for fosfomycin and 28/31 (90%) for pipemidic acid.

Comment: Fosfomycin had good efficacy in the eradication of asymptomatic bacteriuria in pregnancy in a small study. Single dose antimicrobial therapy of asymptomatic bacteriuria in pregnancy is not recommended due to lower efficacy rates compared to multiple-day treatment regimens in the Infectious Diseases of America guidelines

for the treatment of asymptomatic bacteriuria in adults (Nicolle LE 2005). This study is primarily of interest for the safety analysis in pregnancy.

6.3.3.5. Estebanezet al, 2009 (treatment of asymptomatic bacteriuria in pregnancy)

This was an open-label randomised prospective study conducted in Spain of the treatment of asymptomatic bacteriuria in pregnancy. Patients were required to have two positive urine cultures without symptoms at any time during pregnancy. They were randomised to receive either 3g oral fosfomycin single dose or amoxicillin-clavulanate 500 mg/125 mg bd for 7 days. Bacteriological efficacy at 10-14 day follow-up was 44/53 (83%) for fosfomycin and 45/56 (80%) for amoxicillin-clavulanate (p 0.720).

Comment: Fosfomycin had good efficacy in the eradication of asymptomatic bacteriuria in pregnancy in a small study. Single dose antimicrobial therapy of asymptomatic bacteriuria in pregnancy is not recommended due to lower efficacy rates compared to multiple-day treatment regimens in the Infectious Diseases of America guidelines for the treatment of asymptomatic bacteriuria in adults (Nicolle LE 2005). This study is primarily of interest for the safety analysis in pregnancy.

6.3.3.6. Zinner et al, 1990 (treatment of asymptomatic bacteriuria in pregnancy, comparator pipemidic acid)

This was an open-label randomised prospective study conducted in Italy of the treatment of asymptomatic bacteriuria in pregnancy. Patients were randomised to receive either 3g oral fosfomycin single dose or pipemidic acid 400 mg bd for 7 days. Bacteriological efficacy at 10-15 day follow-up was 144/153 (95%) for fosfomycin and 125/138 (91%) for amoxicillin-clavulanate (p NS).

Comment: Fosfomycin had good efficacy in the eradication of asymptomatic bacteriuria in pregnancy in a small study. Single dose antimicrobial therapy of asymptomatic bacteriuria in pregnancy is not recommended due to lower efficacy rates compared to multiple-day treatment regimens in the Infectious Diseases of America guidelines for the treatment of asymptomatic bacteriuria in adults (Nicolle LE 2005). This study is primarily of interest for the safety analysis in pregnancy.

6.3.3.7. Ferreira et al, 2003 (no comparator arm, UTIs in pregnancy)

This was an open-label noncomparative study of acute uncomplicated UTI in females 18-75 years treated with 3g single dose oral fosfomycin. 1021/2524 (29.6%) of the patients were pregnant. Bacteriological efficacy was not reported as many patients did not have follow-up urine cultures performed. Clinical efficacy at day 7 was 3355/3446 (97%).

Comment: Disappointingly, followup urine cultures were not performed in most patients. This trial is primarily of interest for safety analysis as a large number (1021) of pregnant patients were included. See also safety analysis in pregnancy.

6.3.3.8. Ferraro et al, 1990 (comparator norfloxacin, patients 50 years of age or greater)

This is an open-label controlled randomised study of patients with symptomatic uncomplicated UTI in elderly patients (defined as aged 50 years or older). Patients with structural abnormalities, urinary catheterisation or severe renal impairment were excluded. Treatment regimens were either 3g oral fosfomycin as a single dose compared to norfloxacin 400 mg bd for 7 days. Mean age was 68.4 years and 45/60 patients were female. Bacteriological efficacy 25-35 days after the end of therapy was 23/30 (77%) for fosfomycin and 22/30 (73%) for norfloxacin ($p>0.05$).

Comment: Fosfomycin had equivalent efficacy to a standard dosing schedule of norfloxacin in a small open study of UTIs in symptomatic elderly patients. This study is primarily of interest for the safety analysis in the elderly.

6.3.3.9. Pullukcu et al, 2007 (ESBL-producing E coli UTIs, no comparator)

This was an open-label non-comparative retrospective evaluation of the treatment of symptomatic lower UTI caused by ESBL-producing *E coli.* Patients received 3g single dose of oral fosfomycin. Fifty-two patients (25 males, 27 females) with mean age 55.0 (range 19-85 years) were treated. Sixteen patients were uncomplicated, 7 had indwelling urinary catheters, other complicating factors included malignancy, diabetes, renal transplantation (n=5). All isolates were resistant to ciprofloxacin and TMP/SMX. All isolates were susceptible to fosfomycin and carbapenems. Bacteriological efficacy at day 7-9 was 41/52 (78.5%). Clinical and microbiological failure was similar in patients without or with an underlying risk factor or complication ($P > 0.05$, 0/16 versus 3/33; and $P > 0.05$, 4/16 versus 7/36, Fisher's exact test).

Comment: Single dose fosfomycin had good bacteriological efficacy in a retrospective review of 52 patients with TMP/SMX and ciprofloxacin resistant ESBL-producing *E coli* UTIs.

6.3.3.10. Senol et al, 2010 (ESBL-producing E coli UTIs, carbapenem comparator)

This was an open-label non-randomised study of the treatment of symptomatic lower UTI caused by ESBL-producing E coli. Patients received either 3g oral fosfomycin on day 1, 3 and 5 (total of 3 doses) or a carbapenem (IV meropenem 1g tds (n=12) or IV imipenem-cilastatin 500 mg qid (n=8)) for 14 days. Treatment choice was at investigator discretion. Forty-seven patients (19 males, 28 females) with mean age 57.5 were treated. Incidence of complicating factors was 19/27 for fosfomycin and 13/20 for carbapenems (p NS). Most common complicating factors were urinary catheterisation (36.8%), urological surgery (25%) and malignancy (25%). The treatment groups were similar in terms of gender and age. All isolates were resistant to ciprofloxacin and TMP/SMX. All isolates were susceptible to fosfomycin and carbapenems, apart from 1 patient with a fosfomycin-resistant E coli treated with a carbapenem. Bacteriological efficacy at day 7-9 after completion of therapy was 16/27 (59.2%) for fosfomycin and 16/20 (80%) for carbapenems.

Comment: Three doses of fosfomycin had good bacteriological efficacy in a small open-label study of patients with TMP/SMX-resistant and ciprofloxacin- resistant ESBL-producing *E coli* UTIs. Treatment duration for carbapenems is long at 14 days.

6.3.3.11. Neuman and Rufin, 1987 (fosfomycin-resistant UTIs treated with fosfomycin)

This was an interesting open-label non-randomised study of 18 patients (16 female, 2 male) with lower UTIs treated with either fosfomycin 3g single dose (12 patients) or 3g followed by 2g 12-hours later. Urinary isolates were fosfomycin-resistant with MIC of 128-256 mg/L. The study relied on the extremely high urinary levels and prolonged bactericidal activity of fosfomycin in urine. Typical urinary drug levels were not measured in this study but are known from previous studies. Urine cultures were performed on days 0, 3, 7, 14, 21 and 30. Clinical and bacteriological cure was obtained in 12/18 (67%) of patients. Isolates were E coli (14), P mirabilis (2), and Staph epidermidis (2). Reinfection with a new bacterial species occurred in 2 cases, both new isolates had MIC >256 mg/L. Relapse occurred in 2 cases, both E coli and occurred at weeks 2 and 3, respectively. Both strains had developed MIC >256 mg/L. Two patients (one E coli, 1 S epidermidis) had clinical and bacteriological failure. Both of these isolates had an MIC of 256 mg/ml.

Comment: Fosfomycin can be used to treat UTIs which are technically fosfomycin-resistant due to its ability to concentrate in urine with resultant high fosfomycin urinary levels. Of some concern is the fact that 6/18 patients with mildly fosfomycin-resistant isolates either failed treatment or developed high-level fosfomycin resistance after 1 or 2 doses of drug.

6.4. Evaluator commentary: other efficacy studies

6.4.1. Study quality as a group

All studies above were performed in the 1980s and hence are not likely to represent current global antimicrobial resistance patterns, particularly for fluoroquinolones, although in general Australia has lower fluoroquinolone resistance rates than other countries partly due to restrictions on fluoroquinolone usage in this country. Amoxicillin is no longer used first-line for UTIs in Australia due to widespread resistance of E coli. Some of the comparator agents such as pefloxacin and pipemidic acid are of historical interest only. Many of the studies are open-label although some are randomised. Most do not fit GCP guidelines. None of the studies examine resistance development in bacteriological failures, relapses or reinfections. None of the studies have sufficient numbers of pathogens apart from *E coli* to draw any conclusion about efficacy rates for other uropathogens such as *Klebs pneumoniae* or *Staph saphrophyticus.*

6.4.2. Bacteriological efficacy of fosfomycin 3g single dose compared to other antibiotics

Tables below show the pooled data for early (usually 1 week after therapy) and late (usually one month after therapy) bacteriological efficacy for 3g single dose fosfomycin trometamol in the treatment of acute uncomplicated UTI in adult females. When considered as a group, bacteriological efficacy rates for fosfomycin 3g single dose were around 75-94% at one week follow-up and around 60-93% at late (often one month) follow-up. This was mostly comparable or slightly inferior to 5-7 days norfloxacin (2 studies). Only one small study compared fosfomycin to nitrofurantoin and bacteriological efficacy rates were comparable.

Unfortunately, there is no good comparative study for an appropriate dosage schedule of trimethoprim amongst these studies. The single trimethoprim study (Asscher et al 1991) uses a single 200 mg dose of trimethoprim which is too low. Even so, there were no differences in efficacy rates but numbers were small.

Table 15: Randomised, controlled, double-blind, double-dummy treatment studies of fosfomycin trometamol 3g single dose in adult female patients with acute uncomplicated UTI (studies 7.3.1.1-7.3.1.6)*

Study	Ref	Subjects: All	Subjects: N° treated with FT[a]	Subjects: Assessable for efficacy	Reference Therapy	Bacteriological efficacy%: Post-Therapy FT	Post-Therapy Ref[b]	Late follow-up FT	Late follow-up Ref	Adverse Reactions %: FT	Adverse Reactions %: Ref
Selvaggi et al.		89[c]	45	53	Norfloxacin 800 mg; single dose	75	84	-	-	NR[d]	NR[d]
Boerema and Willems		158[c]	79	111	Norfloxacin 400 mg; b.i.d. 7 days	90	98	62	65	13	3
Richaud		62[c]	31	57	Perfloxacin 800 mg; single dose	90	93	86	89	6	6
Asscher and O'Dowd		75	35	69	Trimethoprim 200 mg; single dose	78	61	75	56	6	5
Van Pienbroek et al.		231[c]	116	212	Nitrofurantoin 50 mg; q.i.d. 7 days	81	90	93	87	20	16
Boerema		45	24	30	Amoxycillin 3g; single dose	94	43	71	33	33	38

[a]FT= Fosfomycin trometamol; [b]Ref= reference therapy; [c]multicentre study; [d]NR = none reported

* from Fosfomycin Trometamol Investigator's Brochure Edition 3.0, May 2003.

Table 16: Open-label controlled prospective studies of 3g single dose fosfomycin trometamol in the treatment of adult females with UTI.

Study	n (all)	Fos pts assessable for therapy	Reference	Bacteriological efficacy (%)			
				Early		Late	
				Fos	Ref	Fos	Ref
Pontonnier, 1988	63	33	norflox 400mg bd 5days	94	87	73	78
Raynaert, 1988	32	16	norflox 400mg bd 3 days	88	88	82	56
Jardin, 1987	289	146	pipemidic acid 400mg bd 5d	84	91	93	93

Table 17: Open-label uncontrolled prospective studies of 3g single dose fosfomycin trometamol in the treatment of adult females with UTI.

Study	Fosfo pts assessable for efficacy	Bacteriological efficacy		Adverse events
		Early	Late	
De Caro, 1984*	19	95%	68%	-
Di Nola, 1984*	31	-	97%	8.6%
Moroni, 1987	51	-	80%	5.5%
Rizzo, 1984	10	90%		9.1%
Rolandi, 1984*	9	78%	-	13%
Study Grp Switzerland, 1989*	2158	90%	-	9%

* Included a small number of adult males.

6.4.3. Dose-finding studies

The two dose-finding studies reviewed (Di Nola, 1984; Rolandi, 1984) suggest that in small numbers of patients, two 3g fosfomycin doses 12-hours or 24-hours apart did not improve efficacy. This confirms current knowledge of PK and PD of the drug. Only 10 patients (Di Nola, 1984) received 3g daily for 7-12 days so no conclusions can be drawn from these patients.

6.4.4. Efficacy of fosfomycin in pregnant women with UTIs or asymptomatic bacteruria

In the 7 studies conducted in pregnant patients reviewed in detail, bacteriological efficacy at day 7-14 after fosfomycin 3g single dose in the treatment of asymptomatic bacteruria or UTI ranged from 82-96%. Only 2 studies (Krcemery, 2001; De Cecco and Ragni, 1987) performed urine cultures 4-6 weeks after treatment; these had surprisingly high bacteriological efficacy rates at

4-6 weeks of 95-96% and these rates were mostly substantially higher than the other 5 studies when cultures were performed at 1-2 weeks after treatment. It should be noted that all 7 studies in pregnancy were open-label and had small numbers of patients. The one study (Ferreira, 2003) which included large numbers of patients disappointingly did not repeat urine cultures after treatment.

It should also be noted that single dose antimicrobial therapy of UTIs or asymptomatic bacteriuria in pregnancy is not recommended due to lower efficacy rates compared to multiple-day treatment regimens listed in the Infectious Diseases Society of America guidelines for the treatment of asymptomatic bacteruria in adults (Nicolle LE 2005).

6.4.5. Efficacy of fosfomycin in the elderly with UTIs

One small study reviewed (Ferraro et al, 1990) with patients aged more than 50 years with UTI showed bacteriological efficacy at one month of 77%, comparable to norfloxacin.

6.4.6. Efficacy of fosfomycin against UTis caused by ESBL-producing E coli

The dossier contained 2 open-label studies of patients with UTI caused by TMP/SMX-resistant and ciprofloxacin-resistant ESBL-producing *E coli*. Both contained many patients with complicating factors such as structural abnormalities, malignancy or transplantation. Pullucku et al (2007) was a retrospective review with bacteriological efficacy of 78.5% at day 7-9 after a single 3g dose. Senol et al (2010) demonstrated a bacteriological efficacy rate at day 7-9 of 59.2% after 3g oral fosfomycin on days 1, 3 and 5. Neither study examined resistance development in bacteriological failures, relapses or reinfections.

6.4.7. Efficacy of fosfomycin in fosfomycin-resistant UTIs treated with fosfomycin

The study by Neuman and Rufin (1987) utilises the high urinary concentrations of the drug to treat patients with UTIs which are technically fosfomycin-resistance but have low-level resistant MICs (128-256 mg/mL). In a small study, 12 patients had bacteriological cure but 6 patients had bacteriological failure, relapse or reinfection. All 6 of these patients had highly resistant isolates (MIC>256 mg/mL) after treatment.

6.5. Analyses performed across trials: pooled & meta analyses

6.5.1. Falagas et al, 2010

Literature references contained this meta-analysis of patients with cystitis treated with fosfomycin versus other antibiotics. Randomised controlled comparative trials of uncomplicated lower UTIs which were published prior to 26 October 2009 were assessed. Trials involving patients with pyelonephritis, structural urinary tract abnormalities or other factors predisposing to complicated cystitis such as immunosuppression and malignancy were excluded. Asymptomatic bacteriuria was not an exclusion criteria ie patients could have microbiologically confirmed UTI without symptoms. Twenty-seven published trials were included in the final meta-analysis (8 double-blind, 2 single-blind and 17 open-label RCTs). Pivotal study US-MON-03 was included in its published form (Stein, 1999) but not the unpublished pivotal studies US-MON-01 or US-MON-02. Sixteen of the 27 trials involved exclusively nonpregnant female patients with lower UTIs, 3 involved adult male and non-pregnant females with lower UTIs and 5 of the 27 included trials involved pregnant female patients (3 asymptomatic bacteriuria, 1 lower UTIs and 1 both symptomatic and asymptomatic bacteriuria). The remaining 3 of the 27included trials involving paediatric patients with lower UTIs. Meta-analysis was performed in subgroups of trials of non-pregnant female patients, trials with non-pregnant females and males, trials of pregnant females and paediatric trials.

In all 24 trials in adults, fosfomycin was given as a single 3g dose. In the 3 paediatric trials, single dose either 1g or 2g fosfomycin was given depending on age and weight. In the16 trials involving non-pregnant females, the comparator arms were norfloxacin (4 trials), ciprofloxacin

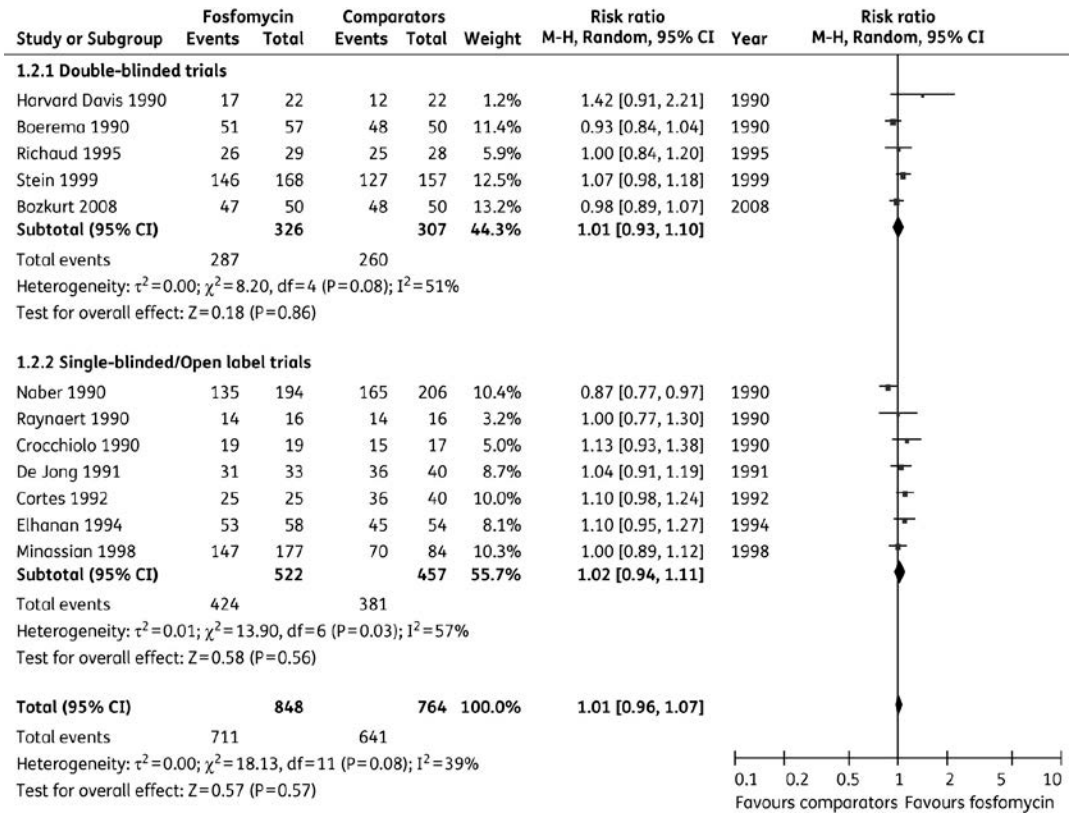
(2 trials), ofloxacin (1 trial), pefloxacin (1 trial), pipemidic acid (1 trial), nitrofurantoin (2 trials), trimethoprim (2 trials), co-trimoxazole (1 trial), cephalexin (1 trial), and amoxicillin (1 trial).

In the 3 trials involving non-pregnant females and male patients, fosfomycin was compared with norfloxacin (1 trial), netilmicin or amikacin (1 trial), and clavulanate-potentiated amoxicillin (1 trial). In the 5 trials involving pregnant women, fosfomycin was compared with amoxicillin/clavulanate (2 trials), ceftibuten (1 trial), pipemidic acid (1 trial) and with nitrofurantoin (1 trial). In the three paediatric trials, fosfomycin was compared with netilmicin (2 trials), and with pipemidic acid (1 trial).

In 5 of the 27 included trials the single-dose fosfomycin treatment was compared with a single-dose treatment of pefloxacin, ofloxacin or co-trimoxazole, norfloxacin, trimethoprim and netilmicin or amikacin, respectively. In the remaining 22 trials, fosfomycin was compared with longer treatment regimens ranging from 3 to 7 days.

In the 16 trials of uncomplicated UTIs in non-pregnant female patients, no difference in clinical success was observed in the comprehensive analysis including all the evaluated comparators (10 RCTs, 1657 patients, RR=1.00, 95% CI=0.98–1.03). Similarly, regarding clinical cure, no difference was observed in the comprehensive analysis (7 RCTs, 1272 patients, RR=1.00, 95% CI=0.96–1.03). No difference was observed regarding microbiological success in the comprehensive analysis regarding fosfomycin versus all the comparators combined (12 RCTs, 1602 patients, RR=1.02, 95% CI=0.97–1.07). There was moderate heterogeneity between pooled studies with heterogeneity I2 = 39%). No difference was also observed between patients treated with fosfomycin versus those treated with comparator(s) in the comprehensive analysis regarding microbiological relapse (8 RCTs, 828 patients, RR=0.84, 95% CI=0.50- 1.39) and microbiological re-infection (7 RCTs, (7 RCTs, 748 patients, RR=1.26, 95% CI=0.77–2.02). Also, no difference regarding microbiological success was noted between trials with a double-blind design and the remaining trials (5 RCTs, 633 patients, RR=1.01, 95% CI=0.93-1.10) versus 7 RCTs, 979 patients, RR=1.02, 95% CI=0.94– 1.11, respectively, P=0.71 for the x2 test for subgroup differences. Specific data for microbiological efficacy are shown in Figure 5 below.

Figure 5: Sensitivity analysis regarding microbiological success in double-blind versus single-blind/open-label trials involving non-pregnant female patients with cystitis who were treated with fosfomycin compared with other antibiotic agents (from Falagas et al, 2010)*



* Vertical line indicates no difference between the compared groups. Diamonds indicate pooled RRs (95% CI). Horizontal lines indicate 95% CIs. Squares indicate point estimates; the size of the squares indicates the weight that each individual study had in the meta-analysis.

In the subgroup of trials involving non-pregnant female and male patients, no difference was observed regarding clinical success (3 RCTs, 286 patients, RR=0.98, 95% CI=0.87–1.11). No difference was also observed between patients treated with fosfomycin versus comparators regarding microbiological success (3 RCTs, 218 patients, RR=1.01, 95% CI=0.88–1.17). Data for relapse and reinfection were not sufficient to perform a meta-analysis.

In trials involving pregnant patients, data sufficient to perform a meta-analysis were provided only for microbiological success. Specifically, no difference was observed between patients treated with fosfomycin versus comparators (4 RCTs, 505 patients, RR=1.00, 95% CI=0.96-1.05).

In trials involving paediatric patients, data sufficient to perform a meta-analysis were provided only for microbiological success. Specifically, no difference was observed between patients treated with fosfomycin versus comparators regarding microbiological success (2 RCTs, 209 patients, RR=0.98, 95% CI=0.92–1.05).

Comment: This meta-analysis has appropriately pooled data for studies of the treatment of uncomplicated UTIs in non-pregnant females. Methods were appropriate and trials were stratified by study type (non-pregnant females, males, pregnant females, children) in a reasonable attempt to deal with heterogeneity of patient type. Trials were mostly old (conducted between 1987 and 1999) and single-blind or open-label trials predominated. Results show that single dose 3g oral fosfomycin was clinically and microbiologically equivalent to pooled data for a wide range of commonly used comparator antibiotics (predominantly fluroquinolones, nitrofurantoin, trimethoprim and cotrimoxazole).

In pregnant patients, males, and children, study quality was generally poor with open-label or single-blind trials common. Considerable heterogeneity of clinical condition was noted. Also, numbers of patients were too low for any statistically meaningful result, particularly in the setting of relatively poor quality trials.

6.6. Evaluator's conclusions on clinical efficacy for Indication 1

6.6.1. Summary of clinical efficacy

6.6.1.1. Pivotal efficacy studies

- The dossier contains three pivotal studies MON-US-01, MON-US-02, MON-US-03 performed in the United States between 1991 and 1994. These studies were conducted according to GCP and were prospective, parallel, comparative, randomised, double-blind double-dummy multicentre trials of adult women with acute uncomplicated UTIs. The three studies are of similar design and conduct.
- Study populations for the three pivotal studies are adult females with acute uncomplicated lower UTI. Patients in MON-US-01 and MON-US-02 were aged 18 years or older but in MON-US-03, females aged 12 years or older were included. This study population is the same as requested in the proposed Australian indication "Treatment of acute uncomplicated urinary tract infections in women above 12 years of age".
- Study drug was single dose 3g fosfomycin tromethamine (Monurol) sachet, the same as the proposed Australian formulation.
- Comparator antibiotics were ciprofloxacin 250 mg twice-daily for 7 days (MON-US-01), TMP/SMX 160 mg/800 mg tablet twice-daily for 10 days (MON-US-02) and nitrofurantoin 100 mg bd twice-daily for 7 days (MON-US-03). All comparator antibiotics were well-chosen and of appropriate dosage to treat uncomplicated lower UTI.
- *E coli* was the most common uropathogen, causing 82-86% of the infections in the 3 studies. There were a range of other pathogens with numbers too low to allow any statistically meaningful comparison of comparative efficacy. In particular, there were surprisingly few isolates of *Staph saphrophyticus* in these studies, an organism known to have variable susceptibility to fosfomycin. As this organism is most commonly a uropathogen in young healthy sexually active women (causing "honeymoon cystitis"), patients with this uropathogen are more likely to present to family practitioners than other patients with cystitis. I note that a large number of study sites in all 3 studies were university-based or hospital-based or urology or gynaecology specialists so this may reflect this imbalance.
- Conduct and design of the three pivotal studies was generally good although an analysis by the FDA was somewhat critical of study design in MON-US-01 and MON-US-02. The FDA report was referred to in some detail in the introductory pages of MON-US-03, the last of the 3 studies. The main criticism was that patients who required use of concomitant antibiotics for UTI were not counted as treatment failures and were included in the ITT efficacy analysis. This means that reported efficacy rates for all drug treatments are likely somewhat higher than they should be. This is more important in MON-US-01, in which 25% of fosfomycin patients received concomitant antimicrobials compared to 13% of ciprofloxacin patients ($p<0.01$). In contrast, in MON-US-02, there were no significant differences in concomitant antimicrobials between the the two study treatments (23% for fosfomycin, 19% for TMP/SMX, $p=0.18$). This study defect was corrected in the later study MON-US-03.
- In MON-US-01, bacteriological efficacy of fosfomycin at day 5-11 after treatment was 83%. Clinical and bacteriological efficacy of ciprofloxacin was superior at 99% ($p<0.01$). Recurrence rate at day 12 or longer after therapy was significantly higher at 14% in the fosfomycin patients compared to the ciprofloxacin patients (4%, $p<0.01$).

- In MON-US-02, bacteriological efficacy of fosfomycin at day 5-11 after treatment was 89%. Clinical and bacteriological efficacy of TMP/SMX was superior at 98% (p<0.01). Recurrence rate at day 12 or longer after therapy was 11% for fosfomycin and 6% for TMP/SMX (p=0.09). It should be noted that large numbers of patients (19.5% for fosfomycin and 24% for TMP/SMX) did not have follow-up urinary cultures to check for recurrence.
- In MON-US-03, there were no significant differences between fosfomycin and nitrofurantoin in bacteriological efficacy, recurrences or new infection rates. Bacteriological efficacy of fosfomycin at day 5-11 after therapy was 83% for fosfomycin and 88% for nitrofurantoin (p=0.099).
- None of the 3 pivotal studies MON-US-01, MON-US-02 or MON-US-03 contain much data on antimicrobial susceptibility testing results after therapy and whether resistance development occurred to the study drug. There is some individual patient data in MON-US-03 but is difficult to tease out and appears incomplete. Of particular importance is MON-US-01 which showed a significantly higher recurrence rate for fosfomycin patients compared to ciprofloxacin patients (14% versus 4%, p<0.01). Is the Sponsor able to provide any further antimicrobial resistance data for any of the 3 studies in early and late follow-up urine cultures after therapy? This is of some importance.
- In summary, evidence from the 3 pivotal efficacy studies suggests that in females with acute uncomplicated lower UTI, a single 3g dose of fosfomycin trometamol is as effective as a 7-day oral regimen of nitrofurantoin (100 mg twice-daily), but is less effective than a 7-day oral regimen of ciprofloxacin (250 mg twice-daily) or a 10-day oral regimen of TMP/SMX (160 mg/800 mg tablet twice-daily).

6.6.1.2. Nonpivotal efficacy studies

- Pooled efficacy information from the nonpivotal efficacy studies is discussed above.
- Most of the nonpivotal efficacy studies were performed in the 1980s and hence are not likely to represent current global antimicrobial resistance patterns.
- Many of the studies are open-label although some are randomised. Most do not fit GCP guidelines. None of the studies examine resistance development in bacteriological failures, relapses or reinfections.
- None of the studies have sufficient numbers of pathogens apart from *E coli* to draw any conclusion about efficacy rates for other uropathogens such as *Klebs pneumoniae* or *Staph saphrophyticus.*
- Nevertheless, when considered together, there are some important observations to make from these studies. Most of the studies show bacteriological efficacy rates for fosfomycin 3g single dose as around 75-94% at one week follow-up. This is comparable to the equivalent fosfomycin bacteriological efficacy rates in the 3 pivotal studies of 83-89%.
- Bacteriological efficacy rates for fosfomycin were comparable or slightly inferior to 5-7 days norfloxacin. Only one small study compared fosfomycin to nitrofurantoin and bacteriological efficacy rates were similar. Unfortunately, there is no good comparative study for an appropriate dosage schedule of trimethoprim amongst these studies.
- Based on limited data, bacteriological efficacy rates of single 3g dose of fosfomycin in pregnant women with UTIs appear similar to nonpregnant female adults. It should also be noted that single dose antimicrobial therapy of UTIs in pregnancy is not recommended due to lower efficacy rates compared to multiple-day treatment regimens.
- In one small study in elderly patients with UTIs, bacteriological efficacy of fosfomycin was similar to norfloxacin.

- In three small open-label studies, fosfomycin had useful activity against antibiotic-resistant isolates. A single 3g dose of fosfomycin had 59.2-78.5% bacteriological efficacy against ciprofloxacin-resistant and TMP/SMX-resistant ESBL-producing E coli UTIs, Many of these patients with complicated UTIs or were immunocompromised. Bacteriological efficacy against uropathogens with fosfomycin MICs of 128-256 mg/ml (that is, low level fosfomycin resistance) was 67%. Efficacy was considered to be due to the high urinary concentrations of the drug.
- In the two dose-finding studies, two 3g fosfomycin doses 12-hours or 24-hours apart did not improve efficacy in small numbers of patients. This would be supported by current knowledge of PK and PD of the drug.

6.6.1.3. Meta-analysis

- The dossier contained one meta-analysis by Falagas et al (2010). It appropriately pooled data for studies of the treatment of uncomplicated UTIs in non-pregnant females. Methods were appropriate and trials were stratified by study type (non-pregnant females, males, pregnant females, children) in a reasonable attempt to deal with heterogeneity of patient type. Trials were mostly old (conducted between 1987 and 1999) and single-blind or open-label trials predominated. There were 16 trials of fosfomycin analysed (1657 patients) in adult nonpregnant females with acute uncomplicated UTIs. Results show that single dose 3g oral fosfomycin was clinically and microbiologically equivalent in adult non-pregnant women with acute uncomplicated lower UTIs to pooled data for a wide range of commonly used comparator antibiotics (predominantly fluroquinolones, nitrofurantoin, trimethoprim and co-trimoxazole).
- In the same meta-analysis by Falagas (2010), study quality was generally poor in UTIs in pregnant patients, males, and children. Open-label or single-blind trials were common. Considerable heterogeneity of clinical condition was noted. Also, numbers of patients were too low for any statistically meaningful result, particularly in the setting of relatively poor quality trials.

6.6.1.4. Evaluation of efficacy compared to Sponsor's efficacy summary in "Clinical Overview"

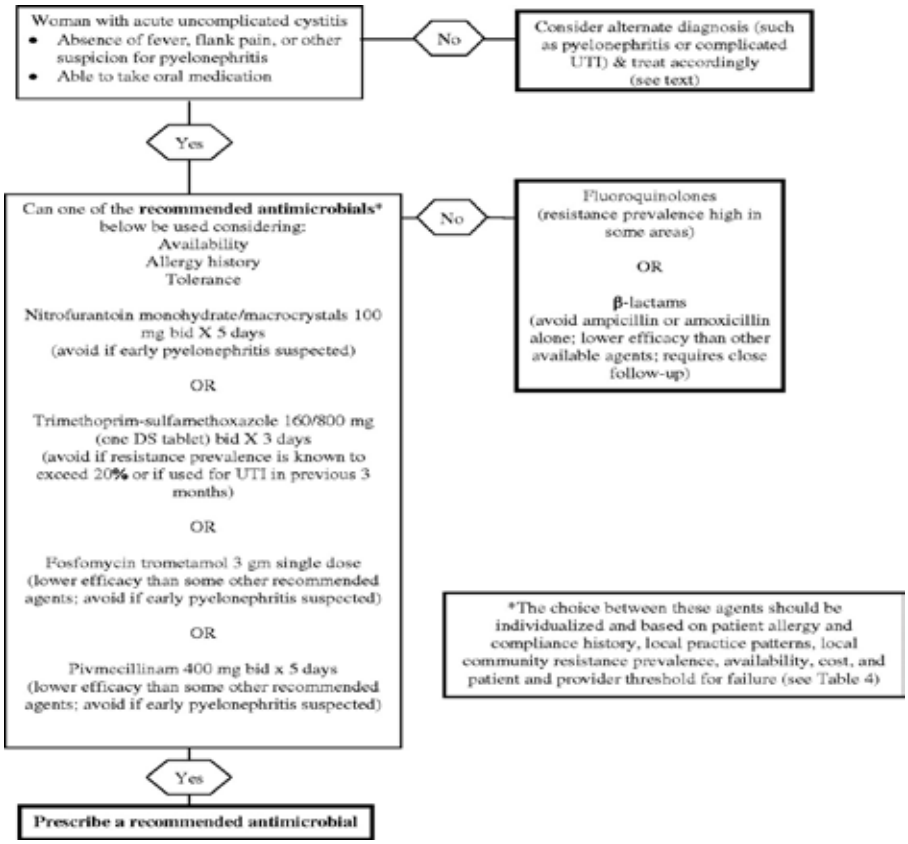
- The Sponsor's efficacy summary is largely accurate and does acknowledge the poor quality and limitations of many of the trials conducted prior to GCP.
- The Sponsor's summary does not mention the FDA's criticism of the studies MON-US-01 and MON-US-02 discussed earlier in this section and the resultant potentially artificially high efficacy rates due to concomitant antimicrobial therapy.

6.6.1.5. Relative place of fosfomycin in therapy of acute uncomplicated UTIs: efficacy considerations and national guidelines in other countries where fosfomycin is approved for usage

- When considering the approval of a novel antimicrobial agent to the Australian market, we need to consider how fosfomycin is being used in the treatment of acute uncomplicated UTIs in countries in which it has been approved for some time and its place in therapy in current medical guidelines in those countries (Grabe 2015; Gupta K 2011; Fosfomycin for urinary tract infections 1997). It is difficult to know to discuss this issue in this report, but this section seems appropriate since relative efficacy compared to other antimicrobials is the most important issue.
- The publication by Gupta (Gupta K 2011) is the publication containing the most recent "International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women" published by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. It states "Fosfomycin

trometamol (3 g in a single dose) is an appropriate choice for therapy where it is available due to minimal resistance and propensity for collateral damage, but it appears to have inferior efficacy compared with standard short-course regimens according to data submitted to the US Food and Drug Administration (FDA) and summarized in the Medical Letter (A-I)". The Medical Letter reference will be discussed further below. The same publication also notes the convenience of a single-dose regimen, and fosfomycin's in vitro activity against ESBL-producing gram-negative rods supported by observational studies but without any randomised controlled trials as yet. The publication incorporates a flow diagram (below) for the treatment of acute uncomplicated UTI. In an Australian context, the diagram would not be the same. For example, trimethoprim would replace TMP/SMX, also pivmevcillman is not available. However, if fosfomycin was to be approved, it could have a similar position in an Australian guidelines, with the same comment "lower efficacy than some other recommended agents, avoid if early pyelonephritis suspected".

Figure 6: Approach to choosing an optimal antimicrobial agent for empirical treatment of acute uncomplicated cystitis (from Gupta et al, 2011)



- The publication in the Medical Letter (1997) referred to Gupta et al (2011) noted the lower efficacy of fosfomycin in the pivotal trials against ciprofloxacin (MON-US-01) and against TMP/SMX (MON-US-02).
- The dossier contains the Guidelines on Urological Infections from the European Association of Urology (Grabe et al, 2015). It notes the following "Antibiotic therapy is recommended (in acute uncomplicated lower UTI) because clinical success is significantly more likely in women treated with antibiotics compared with placebo (LE: 1a, GR: A). The choice of antibiotic therapy should be guided by: spectrum and susceptibility patterns of the aetiological uropathogens; efficacy for the particular indication in clinical studies; tolerability and adverse reactions; adverse ecological effects; cost; availability. According to these principles and the available susceptibility patterns in Europe, fosfomycin trometamol 3 g single dose, pivmecillinam 400 mg tid for 3 days, and nitrofurantoin macrocrystal 100

mg bid for 5 days, are considered as drugs of first choice in many countries, when available (LE: 1a, GR: A) These regimens are recommended for women, but not for men. Most ESBL-producing *E. coli* are still susceptible to fosfomycin. However, in Spain a parallel increase in community use of fosfomycin and resistance to fosfomycin in ESBL-producing *E. coli* has been observed." In these guidelines, it is important to note that fosfomycin is not recommended in any other urological setting, for example, acute uncomplicated UTIs in males, catheter-associated UTIs, complicated UTIs, pyelonephritis, prostatitis, or surgical prophylaxis in urology.

- It is important to note that the relative place in therapy of fosfomycin for the treatment of acute uncomplicated UTI in women in Australia would not be the same as it is in Europe or North America. This is for many reasons including different resistance patterns of uropathogens to trimethoprim, TMP/SMX, fluoroquinolones and beta-lactams. I am simply using the guidelines above to illustrate how the drug is used in other countries ie for which conditions it is considered standard therapy and other indications for which it is not.

6.6.1.6. Evaluator's overall conclusions on efficacy

- Overall there is a large amount of data on efficacy of fosfomycin; the vast majority of this is for a single dose of the 3g oral fosfomycin trometamol sachet that the Sponsor is seeking to have approved.
- There are 3 pivotal efficacy studies from the early 1990s which have been reasonably well-conducted according to GCP. They suggest that single dose 3g fosfomycin trometamol has a clinical and bacteriological efficacy rate of 83-89% in the treatment of females with acute uncomplicated lower UTI. This is as effective as 7 days of nitrofurantoin but less effective than 7-10 days of ciprofloxacin or TMP/SMX.
- The nonpivotal efficacy studies and meta-analysis provide supportive evidence of a similar bacteriological efficacy rate to the pivotal efficacy studies. Most of the studies predate GCP and are open-label with no or poor randomisation methods.
- Bacteriological efficacy of fosfomycin against *E coli* is generally good and this organism is the most common uropathogen. Bacteriological efficacy against other uropathogens especially *Staph saphrophyticus* can be variable.

6.6.1.7. Limitations of efficacy studies

- Potential for and ease of resistance development to fosfomycin after therapy has not been addressed in these studies and is of critical importance to this submission. More information on this area (see questions below and questions in the pharmacodynamics section) needs to be provided for review by the TGA.

6.6.1.8. Questions on efficacy studies

- The placebo sachet in pivotal studies US-MON-01, US-MON-02 and US-MON-03 was matched for appearance with the fosfomycin sachet. A mandarin and / or orange juice flavour plus sweetener was used. Was the placebo sachet also matched for taste?
- In pivotal studies MON-US-01 and MON-US-02, why was it considered necessary to change from a one-tailed to a two-tailed 0.05 level of significance?
- In study MON-US-01, recurrence rates for fosfomycin were higher than for ciprofloxacin. Could the Sponsor provide the results of the susceptibility testing for ciprofloxacin and fosfomycin for the recurrent isolates? Did the recurrent isolates develop resistance to the study drug?
- For study MON-US-02, could the Sponsor provide the results of the susceptibility testing for fosfomycin and TMP/SMX for the recurrent isolates? Did the recurrent isolates develop resistance to the study drug?

- In Studies MON-US-01, are p values available for the comparison between ciprofloxacin and fosfomycin for bacteriological efficacy against E coli?
- In Studies MON-US-02, are p values available for the comparison between TMP-SMX and fosfomycin for bacteriological efficacy against E coli?
- Study US-MON-03 contains the following information: “In its evaluation of the efficacy of FT in the MON-US-01 and MON-US-02 trials, the FDA presented results to an Advisory Committee based on criteria which differed in certain respects from those defined prospectively in the protocols. Primarily, the FDA included the use of antibiotics for UTI as a criterion for failure and data from patients with "missing" visits were handled either by excluding the patient from the modified ITT analysis (for non-completers who discontinued for reasons other than treatment failure or related reasons) or by assigning outcomes on a case-by-case basis (for non-completers who remained in the modified ITT population because their discontinuation reason was related to treatment failure)”.
- Is the Sponsor able to provide the full transcript of the FDA report and also the statistical repeat analysis done according to the FDA recommendations?
- None of the 3 pivotal studies MON-US-01, MON-US-02 or MON-US-03 contain much data on antimicrobial susceptibility testing results after therapy and whether resistance development occurred to the study drug. There is some individual patient data in MON-US-03 but is difficult to tease out and appears incomplete. Of particular importance is MON-US-01 which showed a significantly higher recurrence rate for fosfomycin patients compared to ciprofloxacin patients (14% versus 4%, $p<0.01$). Is the Sponsor able to provide any further antimicrobial resistance data for any of the 3 studies in early and late follow-up urine cultures after therapy?
- In PSUR Jan 1995-Dec 1999, the publication by Licciardello and Bignamini on the efficacy and safety of fosfomycin is missing all Figures. Could the Sponsor provide the full paper including all Figures please?

6.7. Pivotal or main efficacy studies for Indication 2

There were no pivotal studies presented.

6.8. Other efficacy studies for Indication 2

There are only 5 studies in this large dossier in which fosfomycin is used for prophylaxis of UTI. All of these 5 studies are listed in “Literature References”. This is rather surprising and of some importance. It would be expected for an indication to be approved, that there would be at least one pivotal fosfomycin prophylaxis study.

I have reviewed all 5 prophylaxis studies listed. One study is for the prophylaxis of recurrent UTI (Rudenko et al, 2005) and the other 4 studies are for prophylaxis of UTI in surgical and diagnostic procedures.

6.8.1. Study Rudenko et al, 2005 (placebo comparator arm)

This randomised double-blind study was conducted in the Ukraine in a university hospital outpatients department in nonpregnant females aged 16-65 years who had had at least three culture-confirmed lower UTIs in the last 12 months. Patients with severe renal impairment, structural urinary tract abnormalities or antibiotics within the prior 15 days were excluded. Prophylaxis regimens were either a single 3g oral fosfomycin sachet or a single placebo sachet given once every 10 days for 6 months. Sachets were indistinguishable in appearance and flavour. Patients had clinical evaluation and urine cultures at baseline, 60 days, 120 days, 180 days (end of treatment), 270 days and 360 days. The timing of dosing the sachet is not listed in

relation to the timing of taking the urine culture. Compliance with therapy is also not listed. Mean age was 44.6 years in both groups and both groups had had a mean of 4 UTIs in the previous 12 months. *E coli* was isolated in 72.8% of fosfomycin and 75% of placebo patients. Completion rates were good with 158/166 of fosfomycin and 144/151 placebo patients completing the study. UTIs occurred in 8 fosfomycin and 91 placebo patients by day 60 culture ($p<0.001$), 10 fosfomycin and 169 placebo patients by day 120 ($p<0.001$), and 11 fosfomycin and 207 placebo patients by day 180 ($p<0.001$). During the follow-up period (day 180-360), UTIS occurred in 68 fosfomycin and 147 placebo patients by day 270 ($p<0.001$), and 87 fosfomycin and 221 placebo patients by day 360 ($p<0.01$). Antimicrobial susceptibility testing patterns for uropathogens isolated during and after treatment are shown. All 181 during treatment and 299 post-treatment isolates of *E coli* were fosfomycin susceptible. Numbers of other bacterial species were too small to be clinically meaningful but some fosfomycin resistance was seen (post treatment in 3/10 stains *E cloacae*, 3/9 *K pneumoniae*). Importantly, resistance data was not presented by active or placebo arm in the publication.

Table 18: Antibiotic susceptibility of uropathogens isolated before and after fosfomycin prophylaxis (from Rudenko et al, 2005)

[redacted] **Antibiotic susceptibility (%) of 218 uropathogens isolated in the treatment period.**

Pathogens (n)	Drugs				
	FOF	CIP	SXT	NOR	AMC
E. coli (181)	100	84	72	79	88
K. pneumoniae (8)	50	100	87.5	87.5	100
S. saprophyticus (8)	100	100	0	87.5	87.5
C. freundii (10)	100	100	60	70	30
P. mirabilis (7)	100	100	85.5	100	100
Others (4)	50	75	75	75	100
Total (218)					

FOF = fosfomycin; CIP = ciprofloxacin; SXT = co-trimoxazole; NOR = norfloxacin; AMC = amoxicillin + clavulanic acid.

[redacted] **Antibiotic susceptibility (%) of 357 uropathogens isolated in the follow-up period.**

Pathogens (n)	Drugs				
	FOF	CIP	SXT	NOR	AMC
E. coli (299)	100	84	71	79	82
E. cloacae (10)	70	40	20	40	0
S. saprophyticus (18)	100	100	0	94	94
E. fecalis (2)	100	50	100	50	0
P. mirabilis (11)	100	100	82	100	100
K. pneumoniae (9)	67	100	89	100	100
Others (8)	63	75	75	75	87.5
Total (357)					

FOF = fosfomycin; CIP = ciprofloxacin; SXT = co-trimoxazole; NOR = norfloxacin; AMC = amoxicillin + clavulanic acid.

Comment: From the data presented, fosfomycin appears to be an effective prophylaxis for recurrent UTIs in adult females compared to placebo. Many details are missing from this brief publication including compliance with therapy, timing of the dosage compared to timing of urine culture collection (if the sachet was dosed just prior to culture collection, the urine culture would be expected to be sterile) and resistance development in uropathogens stratified by active or placebo arm. More troubling is the theoretical and actual potential for resistance development by the usage of a novel class of antimicrobial such as fosfomycin for prophylaxis.

6.8.2. Periti et al, 1987

This prospective randomised open multicentre study was conducted in Italy in patients undergoing transurethral resection of the prostate (TURP). Patients with UTI or antimicrobial therapy within the preceding 3 days were excluded. There were three prophylaxis arms and in each arm an antibiotic dose was given 3 hours prior to surgery and a second dose was given 24 hours after TURP. Prophylaxis regimens were either two doses of 3g oral fosfomycin, two doses of 3g oral amoxicillin or two doses of trimethoprim/sulphamethoxazole each presented as a trimethoprim/sulphamethoxazole DS tablet. Urine cultures were performed pre-operatively and at day 1, 7 and 14. Median age was 69 years in the amoxicillin and TMP/SMX groups and 68 years in the fosfomycin group. More than 96% of the patients in all 3 arms had benign prostatic hypertrophy and the rest had prostatic carcinoma. More than 80% of the patients in all groups had good general health and 72% had never had a UTI. The three groups were well-matched with no significant differences in baseline parameters.

The incidence of postoperative bacteruria within 2 weeks of surgery was 53/329 (16.4%) for fosfomycin, 79/288 (27.4%) for TMP/SMX and 70/283 (24.7%) for amoxicillin ($p<0.01$ for fosfomycin versus the other 2 arms). The incidence of symptomatic UTI was also significantly less 11/329 (3.3%) for fosfomycin compared to 24/288 (8.3%) for TMP/SMX and 23/283 (8.1%) for amoxicillin ($p<0.01$). The incidence of postoperative fever 38 degrees C or greater was also significantly less at 1/329 (0.3%) for fosfomycin compared to 11/288 (3.8%) for TMP/SMX and 10/283 (3.5%) for amoxicillin ($p<0.01$).

There were 208 UTIs cultured within the 2 weeks postoperative period. The predominant organisms were *E coli* (31.3%), *Pseudomonas* (18.8%), *Klebsiella* (18.8%), and *Proteus* (17.8%). More than 60% of the organisms were "somewhat resistant to the three chosen antibiotics" but more details including resistance patterns stratified by prophylactic antibiotic are not provided.

The same publication includes an open study of 283 patients (52 females, 231 males) who received fosfomycin as prophylaxis for cystoscopy or transurethral resection of vesical papillomas or tumours. The fosfomycin dosing schedule is not specified but presumably is the same as in the TURP study. There was no comparator arm. Postoperative bacteruria occurred in 5/76 (6.6%) of cystoscopy patients and 35/207 (16.9%) of transurethral resection of vesical lesion patients. Of the 40 postoperative UTIs, organisms isolated were *E coli* (37.5%), *Klebsiella* (30%), *Proteus (*7.5%), *Pseudomonas* (7.5%), and *Citrobacter* (10%). Antimicrobial susceptibility testing results are not reported.

Comment: The three-arm open randomised study for TURP prophylaxis. There was significantly less postoperative bacteruria, symptomatic UTI and postoperative fever in the fosfomycin arm compared to the amoxicillin and TMP/SMX arms. Amoxicillin would not be used currently in Australia due to high rates of resistance in E. coli. Unfortunately susceptibility testing results for postoperative uropathogens were not reported although more than 60% of the organisms were "somewhat resistant to the the three chosen antibiotics". Fosfomycin resistance development in patients dosed with fosfomycin is of critical importance. The open study of fosfomycin for prophylaxis of cystoscopy or tranurethral resection of vesical tumours is of less interest as antibiotic prophylaxis is not currently

recommended for these procedures if urine is sterile due to the low incidence of postoperative infection.

6.8.3. Di Silverio et al, 1990

- This open-label prospective study was conducted in 72 Italian urological centres. Patients undergoing transurethral procedures were given a single 3g fosfomycin sachet pre-operatively. There was no comparator arm. Patients were required to have a sterile pre-operative urine culture. TURP patients comprised only 139/712 (19.5%) of the patients. The other procedures were predominantly urethral or vesical papilloma resection or cystoscopy. 20/618 (3.2%) of patients developed UTI by day2 and 22/612 (3.6%) by day 7. Half of these were *E coli* but antimicrobial susceptibility testing is not reported.

Comment: Unfortunately more than 80% of the patients in this open-label study had procedures in which antibiotic prophylaxis is not indicated according to current Australian guidelines if urine is sterile due to the low incidence of postoperative infection (Therapeutic Guidelines Antibiotic 2014). These include resection of urinary papillomas and cystoscopy. Only 19.2% of patients underwent TURP. Results of TURP patients were not presented separately and would be of interest. Fosfomycin susceptibility in post-prophylaxis uropathogens is not reported and would be of interest.

6.8.4. Di Silverio et al, 1988

This is an open-label study of 30 patients undergoing lithotripsy or ureteropyeloscopy. Patients received 3 g oral fosfomycin 3 hours prior to and 24 hours after the procedure. There was no comparator or placebo arm. 2/30 (6%) of patients devloped UTI within 5 days of prophylaxis. Susceptibility testing was not reported.

Comment: Antibiotic prophylaxis is not indicated according to current Australian guidelines for these procedures (Therapeutic Guidelines Antibiotic 2014).

6.8.5. Baert et al, 1990

- This is a randomised double-blind prospective trial conducted at a Belgian hospital of patients undergoing TURP. Prophylaxis arms were an active arm of 3g fosfomycin given on the evening pre-operatively and 24 hours later post-operatively or a placebo arm of identical appearance dosed at the the same times. Patients with antibiotics within the preceding 3 days, more than 3 UTIs in the past year were excluded and patients were required to have sterile preoperative urine culture. Mean age was 69 years (fosfomycin) and 66.1 years (placebo). 55/ 61 patients had benign prostatic hypertrophy. 2/31 fosfomycin patients developed UTI at day 5 culture (both *Acinetobacter,* no susceptibility testing reported) and 7/30 (22%) of placebo patients had UTI by day 5 (p value not reported). None of the patients in either arm had a severe or complicated infection. Of note is that all patients received 2 weeks of nitrofurantoin 100 mg bd starting on day 5 according to the hospital protocol.

Comment: This double-blind study is of historical interest only because antibiotic prophylaxis is now routinely recommended for TURP (Therapeutic Guidelines Antibiotic 2014) ; Grabe 2015). Current Therapeutic Guidelines: Antibiotic recommendations for this procedure are a single dose of IV gentamicin. Of more interest would be a study comparing gentamicin with fosfomycin.

6.9. Analyses performed across trials: pooled & meta analyses

No studies presented.

6.10. Evaluator's conclusions on clinical efficacy for Indication 2

6.10.1. Pivotal efficacy studies

- No studies presented.

6.10.2. Nonpivotal efficacy studies

- Four of the five fosfomycin prophylaxis studies in the dossier are for the proposed indication, prophylaxis of UTIs in surgery or diagnostic procedures of the lower urinary tract in adult males and females. These are all contained in "Literature References".
- In the study by Di Silverio et al (1988), none of the patients have an indication for antibiotic prophylaxis, according to current European and Australian guidelines listed in the next section. In the study by Di Silverio et al (1990), 80% of patients did not have an indication for antibiotic prophylaxis. Results for the patients who did require prophylaxis (predominantly TURP patients) were not presented separately. Hence, one would expect fosfomycin to be equivalent to placebo in 80% of the patients studied, as antibiotics were not indicated in those patients for prophylaxis. Both studies are also poor quality open-label studies.
- The study by Periti et al (1987) was an open randomised study suggesting fosfomycin was more effective than amoxil or TMP/SMX in reducing bacteruria, UTI and postoperative fever in TURP patients. Amoxil is not a good agent for TURP prophylaxis due to relatively poor prostatic penetration of drug. This skews the results as TMP/SMX and amoxil results are combined in the statistical analysis. Hence, no conclusions can be drawn from this relatively poor quality study.
- The study by Baert et al (1990) compares fosfomycin to placebo in TURP patients. This study is of historical interest only as TURP patients now routinely receive antibiotic prophyalxis.

6.10.3. Current Australian and international guidelines on prophylaxis of urinary tract infections in surgery and diagnostic procedures involving the lower urinary tract in adult males and females

- The dossier contains the Guidelines on Urological Infections recently published by the European Society of Urology in 2015 (Grabe, 2015). They contain the following recommendations on role and duration of antibiotic prophylaxis for urological surgery. "Only transrectal core prostate biopsy (Level of evidence: 1b, Grade of recommendation: A) and TURP (Level of evidence: 1a, Grade of recommendation: A) are well documented to require surgical antibiotic prophylaxis. There is no evidence for any benefits of routine antibiotic prophylaxis in shockwave lithotripsy, scrotal surgeries, vasectomies or in standard non-complicated endoscopic procedures, including routine cystoscopies, urodynamic studies, endoscopic removal of tumours or papillomas, and ureteroscopies. Urine cultures are routinely recommended in all urological surgery with directed pre-operative treatment of uropathogens". In the European Guidelines, several antibiotic prophylaxis options are listed for transrectal biopsy (fluoroquinolones, TMP/SMX) and for TURP (TMP/SMX, 2nd or 3rd generation cephalosporin or aminopenicillin with beta-lactamase inhibitor). Fosfomycin is not listed as a therapeutic choice for any urological surgical procedure in the European guidelines despite widespread availability of fosfomycin in Europe since the late 1980s and 1990s. This is because of the paucity of evidence discussed above.
- In the current Therapeutic Guidelines: Antibiotic (Therapeutic Guidelines Antibiotic 2014) the following recommendations for antibiotic prophylaxis in urological surgery are made: For TURP, single dose gentamicin IV is recommended. For transurethral prostatic biopsy, oral ciprofloxacin is recommended. For open or laparoscopic procedures where the urinary

tract is not entered, no prophylaxis is indicated routinely. For open or laparoscopic procedures where the urinary tract is entered, cephazolin is recommended with gentamicin in some circumstances.

6.10.4. Evaluator's overall conclusion on clinical efficacy for Indication 2: Prophylaxis of urinary tract infections in surgery and diagnostic procedures involving the lower urinary tract in adult males and females

- The main current indications in Australia and internationally for antibiotic prophylaxis in procedures involving the urinary tract are in TURP and transurethral prostatic biopsy.
- There were no good quality studies in the dossier of fosfomycin compared to another appropriate antibiotic in the prophylaxis of TURP or transurethral prostatic biopsy.
- Fosfomycin has good prostatic penetration so a good quality study comparing fosfomycin to gentamicin in TURP or fosfomycin to ciprofloxacin in transurethral prostatic biopsy would be of interest.
- Efficacy studies contained in the dossier are of insufficient content and insufficient quality to approve this proposed indication.

7. Clinical safety

7.1. Studies providing evaluable safety data

As both proposed indications utilised the same dosage of fosfomycin trometamol (3g single dose), safety data for both indications has been amalgamated.

7.1.1. Pivotal studies that assessed safety as the sole primary outcome

No studies presented.

7.1.2. Pivotal and/or main efficacy studies

- Study MON-US-01
- Study MON-US-02
- Study MON-US-03

These 3 related pivotal studies had the same methods of collecting and reporting safety data. These are as follows:

- General adverse events (AEs): Safety analyses were performed on all patients who received at least one dose of study medication. These were performed at Visit 2 (day 5-10 of study), visit 3 (day 11-17 for US-MON-01 and US MON-03 and day 14-20 for US-MON-02) and visit 4 (day 18 or later for US-MON-01 and US MON-03 and day 21 or later for US-MON-02). Adverse events were elicited by open-ended questioning and were assessed, documented and reported in accordance with GCP and classified according to MedDRA criteria.
- AEs of particular interest: No adverse events were targeted for specific questioning.
- Laboratory tests: Patients had baseline urinary cultures and urinalysis performed within 96 hours of starting treatment and repeated at Visits 2, 3 and 4. Urinalysis was repeated 4-6 weeks post therapy. Patients had clinical chemistry (urea, electrolytes, liver function, cholesterol and uric acid), full blood count and urinalysis performed within 96 hours prior to starting therapy and repeated at Visit 2 and 3. A central laboratory was used for all 3 studies (SmithKline Beecham Clinical Laboratories) except for urinalyses and urine cultures which were performed by a licensed or accredited local laboratory.

- Other safety variables: Vital signs were recorded at each study visit. Physical examination and body weight were recorded at Visit 1 and the final visit.

7.1.3. Other studies

7.1.3.1. Other efficacy studies

The nonpivotal efficacy studies listed below also provided safety data. Most of the studies were performed in the 1980s and early 1990s prior to the 3 pivotal studies and do not meet GCP guidelines. In general, reporting of safety data was poor and relatively brief and data on adverse events were only collected if the patient spontaneously reported them. Few if any of the studies performed clinical chemistry, haematology or ECG monitoring.

Many of the non-pivotal studies did not specifically list discontinuations due to AEs in the information (usually publications) provided in the dossier. AEs were often not stratified by whether they were probably, possibly or unlikely related to treatment.

Hence, safety data from these studies is often limited at best. Nonpivotal studies which provided safety data are listed here:

- Boerema et al, 1988
- Richaud, 1989
- Asscher, 1991
- Boerema and Groeneveld, 1987
- Van Pienbrook et al, 1993
- Selvaggi, 1990
- Pontonnier, 1988
- Reynaert, 1988
- Dejonckheere, 1988
- Jardin, 1987
- De Caro, 1984
- Di Nola, 1984
- Krejci 1994
- Marini 1984
- Moroni, 1984
- Moroni, 1987a
- Rizzo, 1984
- Rolandi, 1984
- Study Group Switzerland, 1989
- Krcmery, 2001
- Usta, 2011
- Ferreira, 2003

- Ferraro, 1990
- Pullukcu et al, 2007
- Senol, 2010
- Neuman, 1987
- Rudenko et al, 2005.
- Periti et al, 1988.
- Baert, 1990.
- Di Silverio, 1988.
- Di Silverio, 1990.

7.1.3.2. Studies with evaluable safety data: dose finding and pharmacology

No studies submitted.

7.1.3.3. Studies evaluable for safety only

No studies submitted.

7.2. Studies that assessed safety as the sole primary outcome

No studies submitted.

7.3. Patient exposure

All patients in the pivotal studies were female. The majority of the patients in the other controlled and uncontrolled treatment trials were female although some included males. In the four surgical prophylaxis trials, there were both male and female patients. The majority of patients were Caucasian. Most patients had acute uncomplicated lower UTIs although some patients had chronic or recurrent UTIs or asymptomatic bacteruria. Pregnant patients and elderly patients were included in some trials.

The vast majority of patients received a 3g dose of fosfomycin trometamol. A few adolescent females received a 2g sachet in countries where this dosing strength was available. It is likely they received a similar mg/kg dose by body weight compared to adult females.

A few studies included patients dosed with more than one dose of fosfomycin. This was usually 3g daily for 3 doses. Insufficient patients received more than one dose of fosfomycin to be able to make any recommendations or safety analysis for multiple doses of fosfomycin.

Table 19: Exposure to fosfomycin and comparators in clinical studies

Study type / Indication	Controlled studies					Uncontrolled studies	Total Fosfomycin
	Fosfomycin 3g single dose	Nitrofurantoin 100 mg bd x 7 days	Ciprofloxacin 250 mg bd x 7 days	TMP/SMX 1 bd x 10 days	Other comparator		
Indication 1 Pivotal/Main US-MON-01 US-MON-02 US-MON-03	432F 426F 375F*	374F*	445F	428F			1233
Indication 1 Other trial	1810	114(50 mg qid x 7 days)			1715	5580	7390
Subtotal indication 1	3043	488	445	428	1715	5580	8623
Indication 2 Prophylaxis of UTI Nonpivotal trial	1278				752		1278
TOTAL	4321	488	445	428	2467	1480	9901

* Aged 12 years or older; F=female

7.4. Adverse events

7.4.1. All adverse events (irrespective of relationship to study treatment)

7.4.1.1. Pivotal efficacy studies

- **Study MON-US-01.** AEs were reported by 41% of fosfomycin patients and 50% of ciprofloxacin patients. The most frequently reported adverse event was headache which occurred in 8.8% of fosfomycin patients and 9.4% of ciprofloxacin patients. Two AEs were more significantly more common in the fosfomycin group: diarrhoea (7.6% fosfomycin, 4.3% ciprofloxacin, p=0.04) and rash (2.3% fosfomycin, 0.7% ciprofloxacin, p=0.05).
- **Study US-MON-02.** AEs were reported by 46% of fosfomycin patients and 43% of TMP/SMX patients. The most frequently reported adverse event was headache occurring in 11.3% of the patients treated with fosfomycin and 10.7% of the patients treated with TMP/SMX (p=0.83). Diarrhoea was significantly more common in the fosfomycin group: (fosfomycin 9.4%, TMP/SMX 2.6%, p<0.01). Nausea was significantly more common in the TMP/SMX patients (10.0% TMP/SMX, 4.9% fosfomycin, p<0.01) as was rash (5.1% TMP/SMX, 0.7% fosfomycin, p<0.01).

- **Study US-MON-03.** AEs were reported by 51% of fosfomycin patients and 49% of nitrofurantoin patients. The most frequently reported adverse event in the fosfomcyin treatment group was diarrhoea (14.7%) followed by headache (10.1%), and nausea (6.7%). In the nitrofurantoin treatment group, the most frequently reported adverse event was headache (12.0%) followed by nausea (8.6%), diarrhoea (8.0%), and rhinitis (5.9%). Significantly more nitrofurantoin patients than fosfomycin patients reported pruritus (p=0.015); significantly more fosfomycin patients than nitrofurantoin patients reported diarrhoea (p=0.005).
- **Summary of AEs in pivotal efficacy studies.** As the 3 pivotal studies had the same fosfomycin dosage and were of similar study design, pooled data for the 3 studies is shown in the summary of clinical safety provided by the Sponsor.

7.4.1.2. Other efficacy studies

- **Boerema et al, 1988.** AEs were reported in 34% of fosfomycin and 20% of norfloxacin patients. Most common fosfomycin AEs were gastrointestinal intolerance, headache, dizziness.
- **Richaud, 1989.** AEs were reported in 3/31 fosfomycin patients and 2/31 pefloxacin patients.
- **Asscher et al, 1991.** AEs were reported on 2/35 fosfomycin patients and 2/40 trimethoprim patients.
- **Boerema and Groeneveld, 1987.** AEs were reported on 11/24 (46%) of fosfomycin patients and 8/21 (38%) of amoxicillin patients.
- **Van Pienbrook et al, 1993**. AEs were reported on 49/113 (43%) of fosfomycin patients and 28/114 (25%) of nitrofurantoin patients at day 4. At day 9, AEs were reported by 20/102 (20%) of fosfomycin patients and 17/109 (16%) of nitrofurantoin patients. Most common AE in both groups was gastrointestinal intolerance (nausea and diarrhoea).
- **Selvaggi et al, 1990.** No listing for mild to moderate AEs. No severe AEs.
- **Pontonnier, 1988**. AEs were reported in 9/33 fosfomycin patients and 4/30 norfloxacin patients. 7/9 fosfomycin and 2.4 norfloxacin patients had gastrointestinal intolerance.
- **Reynaert, 1988.** AEs were reported in 1/40 fosfomycin patients and 1/40 norfloxacin patients, both gastrointestinal intolerance.
- **Dejonckheere, 1988.** No AEs were noted by spontaneous complaints.
- **Jardin, 1987.** AEs were reported in 25/144 fosfomycin patients and 21/144 pipemidic acid patients, predominantly diarrhoea for fosfomycin (11/144 or 7% of patients) and nausea for pipemidic acid (16/144 or 11% of patients).
- **De Caro, 1984.** No AEs reported in 19 fosfomycin patients.
- **Di Nola, 1984**. 13/152 (8.5%) patients reported AEs, 11 of these were gastointestinal intolerance.
- **Krejci, 1994.** 69/2137 (3.5%) of patients reported AEs. 35 patients reported diarrhoea and 10 reported nausea.
- **Marini, 1984**. 1/39 patients reported an AE, diarrhoea.
- **Moroni, 1987.** 5/91 (5.5%) of patients reported AEs, mostly diarrhoea.
- **Rizzo, 1984**. 1/10 patients reported an AE.
- **Rolandi, 1984.** 5 patients reported gastrointestinal intolerance.

- **Study Group Switzerland, 1989.** 171/2158 (9%) of patients reported AEs. 168/204 adverse events were gastrointestinal intolerance.
- **Rudenko et al, 2005.** AEs were reported in 2/166 of fosfomycin and 4/151 of placebo patients.
- **Periti et al, 1988.** In the 3-arm TURP study, AEs were reported in 12/329 (3.6%) of fosfomycin, 18/283 (6.4%) of amoxicillin patients and 24/288 (8.3%) of TMP/SMX patients ($p<0.05$ for fosfomycin versus amoxicillin and TMP/SMX). 8/12 fosfomycin AEs were mild to moderate gastrointestinal intolerance. In the cystoscopy or transurethral resection of vesical lesion study, 24/283 (8.5%) of fosfomycin patients developed AEs. 20/24 of these were gastrintestintal intolerance.
- **Baert, 1990.** No AEs reported in 31 fosfomycin and 31 placebo patients.
- **Di Silverio, 1988.** One AE was reported in 30 patients.
- **Di Silverio, 1990**. AEs were reported in 24/712 (3.3%) patients. 18/24 (75%) of these were gastrointestinal intolerance.
- **Summary of other efficacy studies**. Pooled data for the non-pivotal treatment studies is shown in "European controlled double-blind double-dummy trials", "open controlled trials", "non-controlled clinical trials", and "prophylaxis studies".

7.4.2. Treatment related adverse events (adverse drug reactions)

7.4.2.1. Pivotal efficacy studies

- **Study MON-US-01.** AEs related to treatment were experienced by 8% of fosfomycin and 6% of ciprofloxacin patients.
- **Study MON-US-02.** AEs related to treatment were experienced by 6% of fosfomycin and 11% of TMP/SMX patients ($p=0.02$). Twenty-one TMP/SMX patients had treatment-related rash and / or urticaria compared to only 2 fosfomycin patients.
- **Study MON-US-03.** AEs related to treatment were experienced by 5% of fosfomycin and 6% of nitrofurantoin patients.

7.4.2.2. Other efficacy studies

- **Boerema et al, 1988.** ADRs probably related to treatment occurred in 13% of fosfomycin and 3% of norfloxacin patients.
- **Richaud, 1989.** ADRs probably related to treatment occurred in 2/31 of fosfomycin and 2/31 of pefloxacin patients.
- **Asscher et al, 1991.** ADRs probably related to treatment occurred in 2/33 of fosfomycin and 2/40 of trimethoprim patients.
- **Boerema and Groeneveld, 1987.** ADRs probably related to treatment occurred in 8/24 of fosfomycin and 8/21 of amoxicillin patients.
- **Van Pienbrook et al, 1993.** ADRs probably related to treatment occurred in 37/113 (33%) of fosfomycin and 14/114 (12%) of nitrofurantoin patients at day 4. At day 9, AEs probably related to treatment occurred in 15/102 (15%) of fosfomycin and 9/109 (8%) of nitrofurantoin patients.
- **Selvaggi et al, 1990.** No listing for mild to moderate AEs. No severe AEs.
- **Pontonnier, 1988**. ADRs probably related to treatment were reported in 9/33 fosfomycin patients and 4/30 norfloxacin patients.

- **Reynaert, 1988.** ADRs probably related to treatment were reported in 1/40 fosfomycin patients and 1/40 norfloxacin patients.
- **Jardin, 1987.** ADRs probably related to treatment were reported in 4/144 fosfomycin patients and 7/144 pipemidic acid patients.
- **Di Nola, 1984.** 11/152 ADRs probably related to treatment were reported.
- **Krejci 1994.** 44/2137 (2.1%) ADRs probably related to treatment were reported.
- **Rudenko et al, 2005**. Treatment-related ADRs were reported in 1/166 fosfomycin patient (rash) and 1/151 placebo patient (rash).
- **Di Silverio, 1990.** Treatment-related ADRs were reported in 16/712 patients.

7.4.3. Deaths and other serious adverse events

There were no deaths in any of the clinical trials contained in the dossier.

7.4.3.1. Pivotal efficacy studies

- **Study MON-US-01.** No deaths. SAES were reported in 3.2% of the fosfomycin treatment group and 4.0% of ciprofloxacin treatment group.
- **Study MON-US-02.** No deaths. SAES were reported in 0.4% of the fosfomycin treatment group and 1.1% of TMP/SMX treatment group. One fosfomycin patient was diagnosed with optic neuritis; this was considered to be a potentially serious adverse event. None of the other serious AEs were treatment-related.
- **Study MON-US-03.** No deaths. SAEs were reported by 5% of fosfomycin patients and 6% of nitrofurantoin patients.

7.4.3.2. Other efficacy studies

- **Boerema et al, 1988.** No deaths. No SAE in fosfomycin group.
- **Richaud, 1989.** No deaths and no SAEs.
- **Asscher et al, 1991.** No deaths and no SAEs.
- **Boerema and Groeneveld, 1987.** No deaths and one SAE in both of the fosfomycin and amoxycillin groups, both diarrhoea.
- **Van Pienhook, 1993.** No deaths and 3 SAEs (3 fosfomycin, 1 nitrofurantoin) were reported. The nature of the SAEs was not reported in the publication.
- **Selvaggi et al, 1990.** No deaths and no SAEs.
- **Pontonnier, 1988**. No deaths and 1 SAE (diarrhoea) in the fosfomycin group.
- **Reynaert, 1988.** No deaths and no SAEs.
- **Dejonckheere, 1988.** No deaths and no SAEs.
- **Jardin, 1987.** No deaths and no SAEs.
- **De Caro, 1984.** No deaths and no SAEs.
- **Di Nola, 1984.** No deaths and no SAEs.
- **Krejci, 1994**. 12/2137 reported SAEs (6 diarrhoea, 1 nausea). No deaths.
- **Marini, 1984.** No deaths and no SAEs.
- **Moroni, 1984.** No deaths and no SAEs.
- **Moroni, 1987.** No deaths and no SAEs.

- **Rizzo, 1984.** No deaths and no SAEs.
- **Rolandi, 1984.** No deaths and no SAEs.
- **Study Group Switzerland, 1989.** 12/1965 (0.6%) patients reported SAEs, 7 of these were gastrointestinal intolerance. No deaths.
- **Rudenko et al, 2005**. No deaths or serious SAEs.
- **Periti et al, 1988**. No deaths or serious SAEs.
- **Baert, 1990.** No deaths or serious SAEs.
- **Di Silverio, 1988.** No deaths or serious SAEs.
- **Di Silverio, 1990.** No deaths or serious SAEs.

7.4.4. Discontinuations due to adverse events

7.4.4.1. Pivotal efficacy studies

- **Study US-MON-01.** Six patients (1.4% fosfomycin, 1.3% ciprofloxacin) in each of the treatment groups were discontinued due to adverse events. Four of the six fosfomycin patients stopped due to gastrointestinal intolerance and one due to rash.
- **Study US-MON-02.**Seven fosfomycin (1.6%) and 18 TMP/SMX (4.2%) were discontinued from the study due to adverse events. The AEs requiring discontinuation from study were gastrointestinal intolerance (3 fosfomycin, 5 TMP/SMX), pregnancy (1 fosfomycin), dry mouth (1 fosfomycin), rash (2 fosfomycin, 13 TMP/SMX). Rash requiring cessation of therapy was much more common in the TMP/SMX patients.
- **Study US-MON-03.**Seven fosfomycin (1.9%) and 16 nitrofurantoin (4.3%) were discontinued from the study due to adverse events. The AEs requiring discontinuation from study were gastrointestinal intolerance and/or abdominal pain (fosfomycin 2, nitrofurantoin 2) and dizziness and/ or CNS toxicity (6 nitrofurantoin). Most of the other discontinutations do not appear treatment-related.

7.4.4.2. Other efficacy studies

Most of the non-pivotal studies did not specifically list discontinuations due to AEs in the information (usually publications) provided in the dossier.

- **Rudenko et al, 2005**. One patient in the fosfomycin and one patient in the placebo arm ceased therapy due to rash.

7.4.5. Safety analyses performed across trials (meta-analysis)

Falagas et al, 2010. This was a meta-analysis of randomised controlled comparative trials of patients with uncomplicated UTIs treated with either single dose 3g fosfomycin (adults) versus single or multiple doses of comparator antibiotics. In trials involving non-pregnant female patients, no difference was observed regarding the occurrence of adverse events in patients treated with fosfomycin versus those treated with comparator(s) in the comprehensive analysis (13 RCTs, 2388 patients, RR=1.25, 95% CI=0.83–1.88). No study withdrawals due to adverse events were observed either in the fosfomycin or comparator group in 11 of the 13 studies (involving a total of 1428 patients) included in the comprehensive analysis. In the remaining two trials patients were allocated to receive either fosfomycin or nitrofurantoin. No difference was observed with regard to the occurrence of study withdrawals due to adverse events, although Falagas noted that study withdrawal due to adverse events was rarely noted in the publications (2 RCTs, 980 patients, RR=2.01, 95% CI=0.05–80.21).

In 3 trials involving non-pregnant female and male patients, the meta-analysis noted no difference in the occurrence of adverse events or study withdrawals due to adverse events (3

RCTs, 297 patients, RR=0.76, 95% CI=0.29–1.96, and 3 RCTs, 297 patients, RR=0.33, 95% CI=0.03–3.08).

In 4 trials involving pregnant patients, the meta-analysis noted adverse events occurred significantly less frequently in pregnant women treated with fosfomycin versus those treated with comparators (4 RCTs, 507 patients, RR=0.35, 95% CI=0.12–0.97). No study withdrawal due to adverse events occurred in either of the compared treatment groups in the three trials that provided relevant data.

In trials involving paediatric patients aged 6 months to 14 years , the meta-analysis noted no adverse event in either of the compared treatment groups in two of the three trials (total of 63 patients treated with fosfomycin) providing relevant data. Similarly, no study withdrawal due to adverse events occurred in either of the compared treatment groups in the three trials involving paediatric patients (183 patients were treated with fosfomycin).

Comment: The meta-analysis noted that detailed data regarding the method of recording and who performed the assessment of the evaluated adverse events were scarcely reported in the included trials, a fact that may have potentially influenced the findings. Study discontinuations due to adverse events were rarely reported. The majority of trials were open-label or single blind though all were randomised.

7.5. Post marketing experience

There is a large amount of post-marketing experience with the drug worldwide. Monurol 3g sachet was approved for use in The Netherlands (1997), UK (1992), USA (1996), Canada (1999), Switzerland (1988) and Singapore (1999). According to the "Summary of Clinical Safety", fosfomycin was approved for the first time in 1986 (Italy) and is authorised in more than 80 EU and non-EU countries. For example, from 1 August 2015 to 31 January 2016, a total of 9,015,221 packages (283,207 packages of 2 g sachets and 8,732,014 packages of 3 g sachets) were sold by Zambon affiliates and contractual partners worldwide. Taking into account that the Defined Daily Dose of fosfomycin for the treatment of noncomplicated lower urinary tract infections is 3 g/one sachet (2 g in paediatric use) as a single dose, the number of subjects who received fosfomycin trometamol during the marketed use is assumed to be approximately equal to the number of packages sold. Therefore, it can be estimated that 9,015,221 patients (283,207 paediatric subjects and 8,732,014 adults) were exposed to fosfomycin trometamol between 1 August 2015 and 31 January 2016.

Two post-marketing surveys enrolling 4295 were included.

Nine Periodic Safety Update Reports (PSURs) conducted by the drug company Zambon are included in the dossier. They cover a continuous period from 1 January 1995 to 31 January 2016.

7.5.1. Severe rare ADRs noted in the postmarketing period possibly or probably related to fosfomycin usage:

The following rare adverse events possibly related to fosfomycin therapy contained in the PSURs should be noted.

7.5.1.1. Hepatic adverse events

- PSUR 1 Jan 1995 - 31 Dec 1999. One case of fatal hepatic necrosis in a patient occurring 7 days after single dose of fosfomycin for UTI. Clinical history, concomitant treatments not available.
- PSUR 1 Jan 1995 - 31 Dec 1999. A case of cholestatic hepatitis in a patient occurring 24 h after single dose fosfomycin. Patient taking multiple other medications including clotiapine.

Resolved within a few days. Patient had previously taken single dose fosfomycin 6 months earlier without incident.

- PSUR 1 July 2000 - 31 July 2005. A patient with cystic fibrosis without liver involvement developed mild to moderate hepatitis 4 days after starting fosfomycin 12g daily (unclear whether oral or IV formulation of fosfomycin used). Resolution on ceasing drug, hepatitis recurred again after 2 further challenges with fosfomycin and resolved when drug ceased. Peak liver enzymes were ALT 921 IU/l, AST 482 IU/l, GGT 214 IU/l.
- PSUR 1 Jan 2005 - 31 Aug 2009. A case of jaundice and hepatitis in a patient two days after 3g fosfomycin. Peak liver enzymes were bilirubin 9.8 x normal, AST 6.3 x normal, ALT 12.4 x normal, GGT 10.8 x normal, ALP 1.4 x normal. Viral hepatitis serology negative.
- PSUR 1 Jan 2005 - 31 Aug 2009. Nonserious hepatic enzyme increase. No other details available.
- PSUR 1 June 2009 - 30 Nov 2009. Hepatitis in a patient without any underlying liver condition and no concomitant medication reported. Three days after fosfomycin administration (unspecified dose for 3 days), the patient experienced drug-induced acute mixed liver damage with peak value ALT 12.8 x upper limit of normal, peak value ALP 1.9 x upper limit of normal, peak value bilirubin 42 µmol/L and peak value GGT 4.9 x upper limit of normal. Therapy with fosfomycin was discontinued and the hepatic function tests normalized 1 week after the withdrawal of the drug.
- PSUR 1 June 2010 - 31 May 2015. Jaundice and hyperbilrubinaemia after 9g daily (ie 3x recommended daily dose) for an unknown amount of time. No other details available.
- PSUR 1 June 2010 - 31 May 2015. Jaundice 48 h after fosfomycin, patient also taking paracetamol and ibuprofen. Recovery after 2 months.
- PSUR 1 June 2010 - 31 May 2015. Acute hepatitis one week after single fosfomycin dose. Liver biopsy showed drug-induced hepatitis.
- PSUR 1Feb 2015- 31 July 2015. Chronic hepatitis, assessed as unlikely related to Monuril, being more probably related to autoimmune origin. No further details provided.
- PSUR 1Feb 2015- 31 July 2015. Patient with medical history of cholecystectomy experienced hepatocellular injury after a single-dose of fosfomycin 3 g. No further details provided.
- PSUR 1Feb 2015- 31 July 2015. Hepatitis. No further details provided.

7.5.1.2. Anaphylaxis / hypersensitivity

- PSUR 1 Jan 1995 - 31 Dec 1999. A case of Quincke's oedema in a patient who received a single dose of fosfomycin and also received enoxacin 200 mg daily for 3 days starting at the same time. Patient recovered.
- PSUR 1 Jan - 30 June 2000 and PSUR 1 July 2000 - 31 July 2005. Two cases of Quincke's oedema which resolved. No other details available.
- PSUR 1 Jan 1995 - 31 Dec 1999. A case of bronchospasm and anaphylactic hypotension in a patient after treatment with single dose fosfomycin. Patient recovered with adrenaline and steroids. No other concomitant medications. Patient had previously had anaphylaxis with beta-lactams and subsequently developed an unspecified allergic reaction with Baycip (ciprofloxacin).
- PSUR 1 Jan 1995 - 31 Dec 1999. A pregnant patient (16 weeks gestation) who developed bullous rash and mild facial swelling 3 days after single dose fosfomycin. Recovered with steroids. Pregnancy otherwise uneventful.

- PSUR 1 Jan 1995 - 31 Dec 1999. A patient with anaphylactic shock immediately after fosfomycin dose. Recovered. Concomitant long-term tricyclics not implicated and continued these.
- PSUR 1 Jan 1995 - 31 Dec 1999. A patient with anaphylactic shock 5 minutes after receiving IV fosfomycin, aminophylline and hydrocortisone for asthma. Patient recovered.
- PSUR 1 Jan 2005 - 31 Aug 2009. Cyanosis and dyspnoea on the same day as 3g dose of fosfomycin. Fully recovered.
- PSUR 1 Jan 2005 - 31 Aug 2009. A case of swollen lip and cheeks and dyspnoea 24 h after 3fg fosfomycin. Resolved.
- PSUR 1 Jan 2005 - 31 Aug 2009. Anaphylactic shock occurring 30 minutes after single fosfomycin dose. Recovered.
- PSUR 1 Jan 2005 - 31 Aug 2009. Anaphylactic shock and rash occurring one day after single fosfomycin dose. Recovered.
- PSUR 1 June 2009 - 30 Nov 2009. Lip swelling, non-serious. No other details.
- PSUR 1 Dec 2009 - 31 May 2010. Face angioedema, urticaria and dyspnoea on the same day as 3g fosfomycin single dose. Recovered.
- PSUR 1 Dec 2009 - 31 May 2010. A patient with anaphylaxis 10 minutes after 3g single dose fosfomycin. This started as itchiness and exanthema on the trunk and legs 10 minutes after taking Monuril. Thereafter the patient started to feel narrowing of the throat followed by hypotension. The patient was brought to the hospital, where she was administered with antiallergic agents, steroids and adrenaline. The patient recovered without sequelae within 24-48 h.
- PSUR 1 Dec 2009 - 31 May 2010. Non-serious throat tightness. No other details.
- PSUR 1 June 2010 - 31 May 2015. Anaphylactic shock after fosfomycin. Recovered.
- PSUR 1 June 2010 - 31 May 2015. Allergic reaction with urticaria and syncope the day after taking a single dose of fosfomycin. Recovered.

7.5.1.3. Cutaneous reactions

- PSUR 1 Jan 2005 - 31 Aug 2009. Toxic skin eruption requiring 7 days hospitalisation. Resolved.
- PSUR 1 Jan 2005 - 31 Aug 2009. Toxic skin eruption starting 24 h after fosfomycin. Resolved.
- PSUR 1 June 2009 - 31 Nov 2009 p14. Toxic skin eruption and fever starting 24 h after fosfomycin, lansoprazole and trimebutine. Resolved.
- PSUR 1 June 2010 - 31 May 2015. 44 cases. Severe cutaneous adverse reactions.

7.5.1.4. Haematological adverse events

- PSUR 1 Jan 1995 - 31 Dec 1999. A patient with UTI took a single dose of fosfomycin and also took nitrofurantoin one day earlier and two subsequent nitrofurantoin doses. Three days after fosfomycin she was admitted to hospital with acute pyelonephritis and was noted to be moderately neutropenic (white call count 1.7 x 10^3/ml) and mildly thrombocytopenic (platelet count 127 x 10^3/ml). Recovered with filgrastim. Neutropenia and thrombocytopenia are both well known as untoward effects following nitrofurantoin administration and they are reported in the information leaflet of Macrobid.[26]

[26] PDR, 50th Edition, p. 1989, 1996/ABPI Compendium of Data Sheets and Summaries of Product Characteristics, p. 840, 1996/97.

- PSUR 1 Jan 1995 - 31 Dec 1999. One case of severe thrombocytopenia in a patient occurring 3 days after single dose fosfomycin. Patient was on multiple other medications including quinidine. Platelet count prior to fosfomycin unknown. Epstein-Barr virus serology IgM positive, later became negative. Thrombocytopenia resolved after platelet transfusion.
- PSUR 1 Jan 1995 - 31 Dec 1999. A patient with small cell lung cancer developed fatigue and was noted to have aplastic anaemia on bone marrow biopsy. This occurred about 2 weeks after single dose of fosfomycin with itraconazole 1g daily g for 6 days started on the same day. The patient died about 4 weeks after bone marrow biopsy with unknown cause of death.
- PSUR 1 Jan 2005 - 31 Aug 2009. Thrombocytopenia. Patient also taking ciprofloxacin. No further details available.
- PSUR 1 Jan 2010- 31 May 2015. Increased INR (3 cases). No further details provided.
- PSUR 1 Jan 2010- 31 May 2015. Decreased INR. No further details provided.
- PSUR 1 Aug 2015 - Jan 2016. Decreased INR. No further details provided.

7.5.1.5. Cardiac adverse events

Many of the early reports of tachycardia occurred in association with a hypersensitivity reaction. However, from PSURs from 2010 onwards, cases of tachycardia without associated hypersensitivity were noted.

- PSUR 1 June 2010 - 31 May 2015. Nonserious tachycardia. No further details.
- PSUR 1 June 2010 - 31 May 2015. Tachycardia, patient also taking Urispas. No further details.
- PSUR 1 June 2010 - 31 May 2015. Tachycardia judged related to fosfomycin in light of temporal association and positive rechallenge. No further details.
- PSUR 1 June 2010 - 31 May 2015. Tachycardia. No further details.
- PSUR 1 Feb 2015 - 31 July 2015. Nonserious tachycardia, fatigue, redness and swelling on the face. No further details.
- PSUR 1 Jan 1995 - 31 Dec 1999. A patient with idiopathic cardiomyopathy and atrial tachcardia six days after single dose fosfomycin. No concomitant medication. Outcome unknown.

7.5.1.6. Vestibular disturbance and deafness

Serious cases of deafness reported in PSURs are:

- PSUR 1 Jan 1995 - 31 Dec 1999. A patient took three 3g fosfomycin doses over a 6 day period and developed severe dizziness during therapy with vertigo and horizontal nystagmus. Bilateral vestibular loss was noted. The patient was referred to an otolaryngologist who noted symptom onset (mild) prior to fosfomycin. Vertifo was severe and lasted several months.
- PSUR 1 Jan 1995 - 31 Dec 1999. A patient who experienced hearing loss following 3 grams of fosfomycin trometamol every 15 days for prophylaxis of recurrent urinary infection for a 2 year period (off-label indication). Resolved.
- PSUR 1 Jan 1995 - 31 Dec 1999. A patient who experienced sudden deafness of left ear, resonance and tinnitus the day after Monuril intake (3 g single dose). Visit to an E.N.T. specialist revealed slightly cicatricial eardrum, decrease in hearing at the bass tones, with balance trouble. The event resolved completely. No further details are available.

- PSUR 1 Jan 2005 - 31 Aug 2009. One case of reversible hearing loss. No other details available.
- PSUR 1 June 2009 - 30 Aug 2009. Non-serious vertigo. No other details.

7.5.1.7. Clostridium difficile colitis

- PSUR 1 July 2000 - 31 July 2005. A case of severe *Clostridium difficile* pseudomembranous colitis in a patient occurring 3 weeks after single dose fosfomycin. Resolved without surgery.
- PSUR 1 Jan 2005 - 31 Aug 2009. Nonserious pseudomembranous colitis. No other details available.

7.5.1.8. Bone and joint adverse events

- PSUR 1 Jan 1995 - 31 Dec 1999. One case of fever, rash, arthralgia and myopathy in a 60-year old female occurring 4 days after fosfomycin. Resolved with corticosteroids and antihistamines. Clinical history, concomitant treatments not available.
- PSUR 1 Jan 2005 - 31 Aug 2009. Allergic cutaneous vasculitis with oligoarthritis in a patient occurring 24 h after single dose fosfomycin. Patient remained bedridden at the time of the writing of the report.
- PSUR 1 Jan 1995 - 31 Dec 1999. Arthralgia, no other details available.

7.5.1.9. Paraesthesias

Paraesthesias are noted in the early reports in the setting of hypersensitivity. However, from PSURs from 2010 onwards, a type of paraesthesia is noted which is frequently oral.

- PSUR 1 June 2010 - 30 May 2015. Paresthesia occurring 15 minutes following the intake of fosfomycin and paracetamol. The available information does not allow any evaluation regarding the nature of the reported events and their causality to fosfomycin.
- PSUR 1 June 2010 - 30 May 2015. Paresthesia occurred in a patient with medical history of anxiety treated with citalopram and zolpidem. The available information does not allow any evaluation regarding the nature of the reported events and their causality to fosfomycin.
- PSUR 1 June 2010 - 30 May 2015. Paresthesia judged possibly related to fosfomycin treatment in light of temporal relationship.
- PSUR 1 June 2010 - 30 May 2015. Paresthesia and diarrhoea judged possibly related to fosfomycin treatment in light of temporal relationship.
- PSUR 1 June 2010 - 30 May 2015. Oral paresthesia reported in a pattern of hypersensitivity.
- PSUR 1 June 2010 - 30 May 2015. Possible paresthesia due to fosfomycin.
- PSUR 1 Feb 2015 - 31 July 2015. Tingling in mouth and cheek. No further details.

7.5.1.10. Other miscellaneous adverse events

- PSUR 1 Jan 2005 - 31 Aug 2009. A case of pancreatitis which resolved after 3 days. Patient was also taking Cycleane 30 oral contraceptive.
- PSUR 1 Jan 2005 - 31 Aug 2009. A patient with Parkinson's disease on longterm levodopa and tramadol. Patient took single dose of fosfomycin with the laxatives macrogol and mebeverine. Diarrhoea with electrolyte disturbance (unspecified) occurred the same day with loss of consciousness requiring 3 days intubation. Recovered.
- PSUR 1 Feb 2015 - 31 July 2015. Unilateral optic neuritis considered unlikely related to the single dose fosfomycin administration, taking into consideration that drug induced optic neuropathy usually occurs in both eyes. No further details provided.

7.5.1.11. Fosfomycin use in pregnancy

- PSUR 1 Jan 1995 - 31 Dec 1999. A case of fetal death in utero (FDIU) at 30 weeks gestation in a patient. Foetal hypotrophy noted on ultrasound at 26 weeks. Patient had had a car accident requiring hospital admission at 28 weeks and received a single dose of fosfomycin at 29.5 weeks, 5 days before ultrasound showing no foetal heart sounds. Patient had placenta praevia with multiple placental infarctions on delivery of the placenta. FDIU considered by the treating physician to be unrelated to fosfomycin.
- PSUR 1 Jan 1995 - 31 Dec 1999. A patient had a FDIU at 7 months gestation two days after two doses of nitrofurantoin and one day after a single dose of fosfomycin. Patient had dark urine and contractions prior to fosfomycin dose.
- PSUR 1 July 2000 - 31 July 2005. A patient with a history of 4 previous abortions, one of which was a trisomy 15 received fosfomycin trometamol 3 grams one dose at week 14 and one at week 18 of gestation. On June 2002, the patient delivered a baby with a congenital left pyelocalyceal dilatation. Pyelocalyceal dilatations are often an effect of a congenital vesico-ureteral reflux, a quite common disease diagnosed in 17-37% of prenatal ultrasounds. It is considered that an association with fosfomycin is possible but unlikely.
- PSUR 1 Jan 2005 - 31 Aug 2009. A pregnant patient took a single 3g dose of fosfomycin at 12 weeks of gestation. Ultrasound performed the same week showed spina bifida.
- PSUR 1 Dec 2009 - 31 May 2010. A pregnant patient took a single 3g dose of fosfomycin at 12 weeks of gestation. Child born with hydrocele and small penis size.

7.5.1.12. Prescription-event monitoring report

- PSUR 1 Jan 1995 – 31 Dec 1999 contains a 1997 prescription-event monitoring report from the Drug Safety Research Trust, a registered UK charity. This was conducted in a cohort of 3,363 patients. The exposure data was prescriptions collected by the Prescription Pricing Authority (PPA) in England. The outcome data were event reports obtained by sending questionnaires (green forms) to the general practitioners who issued prescriptions for fosfomycin. In this particular study, the fosfomycin prescriptions were written during the period February 1994 to June 1996 and the green forms were posted approximately 6 months later.
- 3,783 (45%) of the 8,303 green forms posted were returned. 929 (39%) of the 2,382 general practitioners (GPs) who were sent green forms failed to return any of them. 420 (11%) of the 3783 green forms that were returned were classified as void because they did not contain any clinical data. Therefore useful information is available on a cohort of 3,363 patients (41% of all fosfomycin prescriptions during in the 29-month period).
- Age and sex: Of the 3,363 patients, 286 (9%) were males with a mean age of 57 ± 19.4 years and 3,033 (90%) were females with a mean age of 46 ± 19.7 years.
- Indications: A study of the indications for which the drug was prescribed shows that the major usage was for urinary tract infection/cystitis (76%). The indication was not specified for 18% of the patients.
- Effectiveness: 2,993 (89%) of the total cohort included an opinion about the effectiveness of fosfomycin. Fosfomycin was perceived by GPs to have been effective in 2,668 (89%) of these and not effective in 325 (10.9%) of patients.
- Selected events of interest: The incidence of diarrhoea was more than 1.0 per 1000 patients. Two cases of skin reaction (one facial rash with eye swelling within 48 h of taking the drug and one body rash). One case *Clostridium difficile* diarrhoea, patient also received other unspecified IV antibiotic within the same 24 h period.
- Discontinuations: Not applicable as fosfomycin is administered as a single dose.

- Pregnancies: There were a total of 30 pregnancies reported. Thirteen women had taken fosfomycin during pregnancy, two of these were in the first trimester. The outcomes of these pregnancies were 12 live births and one spontaneous abortion. One baby exposed to fosfomycin four days before delivery was born with congenital adrenal hyperplasia.
- Deaths: There were a total of 57 deaths (1.7% of the cohort). No death was attributed to fosfomycin.

7.6. Evaluation of issues with possible regulatory impact

Unlike most new drug submissions, fosfomycin has been commercially available and widely used in many countries in Europe, the United States and elsewhere since the 1980s. Hence, in addition to the clinical trial data discussed, there is a very large postmarketing experience of the drug which is contained in the PSURs in the dossier. These are discussed in detail in this report and the information from these are included here for convenience and to collate all the data in one place, as they provide useful and additional detail about rare and important adverse events with possible regulatory impact.

It should be noted that patients in the 3 pivotal studies had haematology and biochemistry testing performed at baseline and repeated at day 5-9 and day 11-15 only. Also, it was uncommon for haematology or biochemistry testing to be performed in the nonpivotal studies. No clinical study in the dossier including electrocardiographic monitoring. Most clinical studies in the dossier were performed in the 1980s or 1990s predating GCP. Hence, and unusaully for a novel drug application, most rare issues with potential regulatory impact will likely be identified by the post marketing experience.

7.6.1. Liver function and liver toxicity

7.6.1.1. Pivotal efficacy studies

- **Study US MON-01.** A shift analysis was done for the twelve serum chemistry parameters (including liver function tests) evaluated to determine the number of patients in each treatment group who had normal pre-treatment values and abnormally elevated post-treatment values. In the fosfomycin and ciprofloxacin treatment groups, zero to five of the patients experienced a shift from a normal test value to an abnormally elevated value (pre-treatment to post-treatment) for eleven of the twelve serum chemistry parameters evaluated. Two fosfomycin patients had an elevated SGOT value that exceeded 150 U/L. One patient taking only the oral contraceptive pill with baseline normal liver function had hepatitis with liver enzymes of SGOT 666 IU/l and SGPT 213 IU/L and normal bilirubin and alkaline phosphatase at visit 3. The liver enzymes had normalised at week 12.
- **Study US-MON-02.** A similar shift analysis was done in the same manner as for US-MON-01. One fosfomycin patient had a mild elevation of SGOT and SGPT.
- **Study US-MON-03.** A similar shift analysis was done in the same manner as for US-MON-01. In the fosfomycin and nitrofurantoin treatment groups, zero to six patients experienced a shift from a normal test value to an abnormally elevated value (pre-treatment to post-treatment) for eleven of the twelve serum chemistry parameters evaluated. None appear clinically significant. There were no significant changes in liver function in the fosfomycin group.

7.6.1.2. Other nonpivotal studies

Liver function testing was rarely performed and / or reported. No reports of clinical hepatitis.

7.6.1.3. Post marketing experience

Twelve patients with hepatitis are recorded in the PSURs with each case discussed individually. Information on each case is variable. Hepatitis in the 12 cases typically occurs 1-7 days after the

dose. Hepatitis cases in the PSURs were mostly acute and sometimes associated with jaundice. Some cases were cholestatic. Some but not all patients were taking concomitant medications. History of other confounding factors such as alcohol intake is not reported for any case and only 1/12 cases had viral hepatitis serology reported. Most cases were reported to resolve although that information was not uniformly recorded in the PSURs. There was one case of fatal hepatitis necrosis in a 38 year old female (case PSUR 1 Jan 1995-31 Dec 1999 p12, case #24200). No details of her clinical history are available except that it occurred 7 days after single dose of fosfomycin for UTI. No concomitant medications are listed for the fatal case.

"Summary of Clinical Safety" lists 22 serious cases and 3 non-serious cases of adverse reactions casuing hepatobiliary injury from spontaneous reporting and literature review. No further details of cases are provided in the dossier apart from the listing in this table.

7.6.1.4. Summary of liver toxicity

- According to the information contained in the dossier, fosfomycin is associated with hepatitis but it is rare. In the pivotal studies, only 3 fosfomycin patients had hepatitis based on abnormal liver function testing results. Two were asymptomatic and it is unclear whether the third patient had symptoms. In post marketing data contained in the PSURs, hepatitis is reported on 12 occasions with one fatal case. It is unclear whether the fatal case was taking other concomitant medications. The dossier lists 25 cases of adverse reactions causing hepatobiliary injury obtained from spontaneous reporting and literature review. The dossier does not provide further details of the other 13 cases apart from the listing in the table.

7.6.2. Renal function and renal toxicity

7.6.2.1. Pivotal efficacy studies

It should be noted that patients with significant renal impairment at baseline were excluded from the pivotal studies.

- **Study US MON-01.** No significant changes in shift analysis and no markedly abnormal results.
- **Study US MON-02.** No significant changes in shift analysis and no markedly abnormal results.
- **Study US MON-03.** No significant changes in shift analysis and no markedly abnormal results.

7.6.2.2. Other nonpivotal studies

- Renal function testing was rarely performed and / or reported. No reports of clinical renal impairment.

7.6.2.3. Post marketing experience

There were no reports of renal impairment associated with fosfomycin in the PSURs. The "Summary of Clinical Safety" lists 14 serious cases and 27 non-serious cases of adverse reactions causing renal and urinary disorders from spontaneous reporting and literature review. Two serious cases are listed as "tubulointerstitial nephritis". No further details of cases are provided in the dossier apart from the listing in this table.

7.6.2.4. Summary of renal toxicity

- Based on the information contained in the dossier, fosfomycin does not appear to be have a significant association with renal toxicity. As the most common adverse reaction of fosfomycin is gastrointestinal intolerance, prerenal failure due to dehydration from nausea, vomiting and diarrhoea could occur. Details of the 14 serious renal and urinary adverse events listed were not provided.

7.6.3. Other clinical chemistry

7.6.3.1. Pivotal efficacy studies

- **Study US MON-01.** Thirty-three fosfomycin patients and 37 ciprofloxacin patients had a rise in serum cholesterol out of normal range at post-treatment evaluation. The number of shifts from normal to high values was similar in both the fosfomycin and ciprofloxacin treatment groups. The shift from normal to high (max 27.5 mEq/L) in the potassium tests was probably due to a laboratory error (receipt of hemolyzed specimens or plasma rather than serum).
- **Study US-MON-02.** Thirty-five fosfomycin patients and 21 TMP/SMX patients had a rise in serum cholesterol out of normal range. The number of shifts from normal to high values was similar in both the FT and TMP/SMX treatment groups. The shift from normal to high (max 27.5 mEq/L) in the potassium test was probably due to a laboratory error as in Study US-MON-01.
- **Study US-MON-03.** Twenty-eight fosfomycin patients and 31 nitrofurantoin patients had a rise in serum cholesterol out of normal range. The number of shifts from normal to high values was similar in both treatment groups. There were no markedly abnormal results.

7.6.3.2. Other studies

Clinical chemistry results were rarely performed and / or reported. No reports of significant abnormalities.

7.6.3.3. Post marketing experience

There was a single case of pancreatitis in a patient which resolved after 3 days. It is unclear whether this was a clinical and / or biochemical pancreatitis. The patient was also taking an oral contraceptive pill. The following serious abnormalities in the Metabolism disorders tabulation were listed: “hypernatremia 1 case, hyponatremia 4 cases, hypokalemia 2 cases, hypoglycaemia 1 case”. No further details are provided of these cases in the dossier.

7.6.3.4. Summary of clinical chemistry

Based on the information provided in the dossier, fosfomycin does not appear to have a significant association with clinical chemistry abnormalities (this does not include liver and renal function which were discussed). The serum cholesterol abnormalities noted in the 3 pivotal studies are minor, of similar incidence to the 3 comparator antibiotic arms and do not appear clinically significant.

7.6.4. Haematology and haematological toxicity

7.6.4.1. Pivotal efficacy studies

In the pivotal studies, haematology tests were last performed at day 11-15, so long-term haematology effects are unlikely to have been noted within this time interval.

- **Study MON-US-01.** The shift analysis of the hematology data showed that in both treatment groups there was a shift from normal to low levels for hemoglobin, red blood cells, hematocrit, white blood cells, neutrophiils, and Iymphocytes. The number of shifts from normal to low values were few with numbers similar in both treatment groups. Decreases of hemoglobin to below the normal range were the most common changes noted among hematology tests. It is of note, however, that among fosfomycin patients, hemoglobin levels were not very low, they ranged from 11-16.3 g/dL at baseline and from 10.7-16.3 g/dL after therapy (mean change -0.26 g/dL; $p<0.01$) No markedly abnormal hematology values were noted in any of the fosfomycin patients evaluated.
- **Study US-MON-02.** Overall, the number of shifts from normal to low values were few. However, over three times as many shifts in hemoglobin from normal to low occurred in the

TMP/SMX group (25) than in the fosfomycin group (7). Almost twice as many shifts in hematocrit from normal to low occurred in the TMP/SMX group (15) than in the fosfomycin group (8). Decreases of hemoglobin· to below the normal range were the most common changes noted among hematology tests. It is of note, however, that among fosfomycin patients, hemoglobin levels were not very low; they ranged from 10.3 - 16.6 g/dL at baseline and from 10.2 - 15.7 g/dL after therapy (mean change -0.11 g/dL; p<0.01). One fosfomycin patient had developed an eosinophilia of 14% at Visit 3. None of the marked elevations was considered to be clinically significant.

· **Study US-MON-03.** Overall, the number of shifts from normal to low values were few. Decreases of hemoglobin to below the normal range were the most common changes noted among hematology tests. It is of note, however, that among fosfomycin patients, average hemoglobin levels were not significantly low. Just over l% of fosfomycin patients had markedly abnormal WBC counts either high or low (1.4% vs. 0.6% for nitrofurantoin). Further details were not supplied. Eosinophilia is listed as occurring in 57/362 (15.7%) of fosfomycin patients and 58/346 (16.8%) of nitrofurantoin patients (US-MON-03 report in the dossier). These are extraordinarily high results for both drugs. However, on review of the specific listing for eosinophilia, 20 (5.3%) fosfomycin patients and 14 (3.7%) nitrofuranotin patients appear to have had eosinophilia. This is still higher and out of keeping with studies MON-US-01 and Mon-US-02 in which eosinophilia rates were <1%.

Comment: Could the Sponsor please advise the correct rate of eosinophilia for both drugs in Study US-MON-03? If the the rate has risen compared to the two earlier pivotal studies, has the formulation changed? Was any eosinophilia clinically significant?

7.6.4.2. Other studies

Haematology results were rarely performed and / or reported. No reports of clinical issues.

7.6.4.3. Post marketing experience

The PSURs report 3 cases of thrombocytopenia. In each case, the patient was taking another medication which could have caused thrombocytopenia (quinidine, nitrofurantoin, ciprofloxacin respectively). One of these patients also had neutropenia which responded to filgrastatim. Another patient with small cell lung cancer taking concomitant itraconazole developed aplastic anemia and died. Cause of death of this patient was unknown. Five patients developed decreased or increased INR, no further details were provided. The following 23 serious adverse reactions are listed, the most important of which were: agranulocytosis/neutropenia (4), aplastic anaemia/bone marrow failure/ pancytopenia (3), anaemia (1), immune thrombocytopenic purpura (2), leukocytosis (1), leukopenia (2), macrocytosis (1), polycythaemia (1), thrombocytopenia +/- purpura (7).

7.6.4.4. Summary of haematological toxicity

Fosfomycin has been associated with a range of haematological toxicities but all appear to be rare. The most common of the rare toxicities are eosinophilia, thrombocytopenia, neutropenia and panyctopenia. Interestingly the high (if correct) rates of eosinophilia noted in pivotal study US0MON-03 are not reflected in post-marketing surveillance, which have no reports of eosinophilia (possibly because eosinophilia is rarely symptomatic unless associated with allergic rash).

7.6.5. Electrocardiograph findings and cardiovascular safety

7.6.5.1. Pivotal efficacy studies

No electrocardiograph monitoring was performed in the 3 pivotal studies.

7.6.5.2. Other studies

No electrocardiograph monitoring was performed in the nonpivotal studies.

7.6.5.3. Post marketing experience

In the PSURs, 6 cases of tachycardia were noted, one of which recurred after challenge. 20 serious cardiac disorders are listed, the most important of which were arrhythmia (1), atrial fibrillation/tachycardia (2), bradycardia (1), tachycardia (6), sinoatrial block (1), torsades de pointes(1).

7.6.5.4. Summary of electrocardigraph findings and cardiovascular safety

Electrocardigraph monitoring was not performed during the clinical trials of fosfomycin. No QT/QTc studies were submitted. Based on the postmarketing data, the drug does not appear to be associated with significant cardiac toxicity.

7.6.6. Vital signs and clinical examination findings

7.6.6.1. Pivotal efficacy studies

- **Study US-MON-01.** In both the fosfomycin and ciprofloxacin populations, statistically significant, but clinically insignificant decreases from mean baseline values were noted for systolic blood pressure and temperature.
- **Study US-MON-02.** In both the fosfomycin and TMP/SMX populations, statistically significant, but clinically insignificant decreases from mean baseline values were noted for diastolic blood pressure and temperature.
- **Study US-MON-03.** In both the fosfomycin and nitrofurantoin populations, statistically significant, but clinically insignificant decreases from mean baseline values were noted for temperature. In the fosfomycin population, statistically significant decreases from mean baseline values were noted for diastolic blood pressure and sitting pulse. These decreases were not considered to be clinically significant.

7.6.6.2. Other studies

No reports of clinically important issues.

7.6.6.3. Post marketing experience

No reports of concern in the PSURs.

7.6.6.4. Summary of vital signs and clinical examination findings

No significant abnormalities noted.

7.6.7. Immunogenicity and immunological events including hypersensitivity

7.6.7.1. Pivotal efficacy studies

No immunological events apart from rash were noted in the 3 pivotal studies.

7.6.7.2. Other studies

No immunological events apart from rash were noted.

7.6.7.3. Post marketing experience

The PSURs contain 7 reports of anaphylactic shock and/ or hypotension following fosfomycin. Onset after dosing was usually not specified but one case occurred 5 minutes after IV fosfomycin, one case stated 10 minutes after an oral dosage and another case 30 minutes after an oral dosage. Three cases of Quincke's oedema were noted and 6 cases of facial or lip oedema. There were also cases or urticaria, cyanosis and dyspnoea. Nine cases of angiooedema, 12 cases of anaphylaxis, 15 cases of dyspnoea and 10 cases of unspecified hypersensitivity are noted without further detail.

7.6.7.4. Summary of immunological events including hypersensitivity

Fosfomycin is clearly associated with immediate hypersensitivity in the form of anaphylaxis, angiooedema, urticaria and asthma-like reactions. These are well-described but appear rare from the data contained in the dossier.

7.6.8. Serious skin reactions

7.6.8.1. Pivotal efficacy studies

Rash was reported in the 3 pivotal studies but there were no serious skin reactions noted.

7.6.8.2. Other studies

Rash was reported but there were no serious skin reactions noted.

7.6.8.3. Post marketing experience

There were 3 cases of toxic skin eruptions noted in the PSURs. The following serious skin reactions were noted: photosensitivity (3), erythema multiforme (2), Stevens Johnson syndrome (1), drug reaction with eosinophilia and systemic symptoms (2) and toxic epidermal necrolysis (2).

7.6.8.4. Summary of serious skin reactions

From the data contained in the dossier, fosfomycin is associated with serious skin reactions but these are rare.

7.6.9. Severe gastrointestinal disturbance and / or Clostridium difficile colitis

7.6.9.1. Pivotal efficacy studies

Eight patients in the pivotal efficacy studies who received fosfomycin discontinued due to gastrointestinal intolerance, with diarrhoea the most notable symptom. Duration of diarrhoea in these discontinuationed patients was 1-7 days. None of the patients required hospitalisation.

7.6.9.2. Other studies

No reports of note.

7.6.9.3. Post marketing experience

In the PSURs, there were 2 case reports of *Clostridium difficile* infection which resolved without surgery. There were 3 reports of this condition.

7.6.9.4. 8.6.9.4. Summary of severe gastrointestinal disturbance or Clostridium difficile colitis

Diarrhoea is a relatively common fosfomycin adverse reaction but severe gastrointestinal disturbance is uncommon and *Clostridium difficile* infection appears rare.

7.6.10. Vestibular disturbance and deafness

7.6.10.1. Pivotal efficacy studies

No reports noted.

7.6.10.2. Other studies

No reports noted.

7.6.10.3. Post marketing experience

The PSURs contain one report of vertigo, vestibular loss and horizontal nystagmus lasting several months. There was another case of non-serious vertigo. There were 2 cases of reversible hearing loss. There was another report of reversible hearing loss in a patient taking fosfomycin

every 15 days over a 2-year period (for an off-label indication). The following serious adverse reactions are listed: deafness (4), tinnitus (2), vertigo/vestibular disorder (6).

7.6.10.4. Summary of vestibular disturbance and deafness

Fosfomycin is associated with deafness, tinnitus, and vestibular disorder but these adverse events appear rare.

7.6.11. Psychiatric disturbance

7.6.11.1. Pivotal efficacy studies

No reports noted.

7.6.11.2. Other studies

No reports noted.

7.6.11.3. Post marketing experience

No reports in the PSURs. The following important serious adverse reactions are listed: acute psychosis (1), agitation (1), confusional state (2), hallucination (1), hypervigilance (1), insomnia (2), restlessness (1).

7.6.11.4. Summary of psychiatric disturbance

No significant adverse reactions noted in the dossier.

7.6.12. Bone and joint disturbance

7.6.12.1. Pivotal efficacy studies

No reports noted.

7.6.12.2. Other studies

No reports noted.

7.6.12.3. Post marketing experience

The PSURs contain 2 case reports of arthralgia and 1 case of oligoarthritis. 4 cases of arthralgia are listed.

7.6.12.4. Summary of vestibular disturbance and deafness

No significant adverse reactions noted in the dossier.

7.6.13. Neurological disturbance including paraesthesias

7.6.13.1. Pivotal and/or main efficacy studies

No events noted except one patient diagnosed with optic neuritis in Study US-MON-02 at day 10. Her vision returned to normal after steroid therapy.

7.6.13.2. Other studies

No reports noted.

7.6.13.3. Post marketing experience

Seven cases of paraesthesias noted in the PSURs. The paraesthesias are most commonly noted as tingling in the mouth, tongue and cheek. There are 16 cases of paraesthesias noted although only 2 are severe. Dysgeusia was noted in 11 cases although only 1 case was severe. There was also one case of hypogeusia. There was one case of optic neuritis listed. No other neurological disturbances of concern are in the dossier.

7.6.13.4. Summary of neurological disturbance including paraesthesias

Paraesthesias and abnormalities of taste occur but are usually mild and transient.

7.7. Other safety issues

7.7.1. Safety in pregnancy

7.7.1.1. Safety in studies conducted in pregnant patients with UTIs or asymptomatic bacteruria

The dossier contains nine clinical studies in which at least 1387 pregnant patients with either symptomatic lower UTI or asymptomatic bacteruria are treated with fosfomycin, usually 3g single dose. All of the studies are open-label and they are mostly small but they are important for consideration of safety of fosfomycin in pregnancy. Gestational age at treatment was not always specified but only the studies by Estebanezet (2009) and Ferreira (2003) appear to include patients in the first trimester. Examination of offspring at birth or followup of the baby after birth was not commonly reported. Details of the studies are as follows:

- **Study Moroni, 1984.** In the study by Moroni, fosfomycin 3g was given in one dose (10 patients) or two doses (3 patients) to pregnant women in the second or third trimester. Seven patients had UTIs and six had asymptomatic bacteriuria. Bacterial eradication occurred in 12/13 patients. One patient developed diarrhoea. Patients were followed to 20-40 day urine cultures only, there is no mention of the health or otherwise of the offspring after delivery.
- **Study Bayrak et al, 2007**. In this study conducted in a university hospital in Turkey, patients in 2nd trimester with asymptomatic bacteriuria received with 3g oral fosfomycin (44 patients) or cefuroxime 250 mg bd for 5 days (40 patients). Gestational age was a mean of 16 +/- 2 weeks for fosfomycin and 16.2 +/- 2.4 weeks for cefuroxime. Last patient review was only 7 days after treatment although the patients did deliver in the same university hospital. One fosfomycin patient developed skin rash and two cefuroxime patients developed candidiasis. No other adverse event or adverse pregnancy outcomes were noted in the publication.
- **Study De Cecco and Ragni, 1987.** This study was conducted in Italy of the treatment of asymptomatic bacteriuria in pregnancy gestation week 8 or later. Single 3g dose of fosfomycin was compared to pipemidic acid. 52 women received fosfomycin, early results only are presented in the publication. Gestational week of dosing is not mentioned. Patients were reviewed 4 weeks after treatment for repeat urine culture. The publication states “we found no side effects worth mentioning either from the clinical or biological point of view”. Whether any additional review of the mothers or babies occurred apart from the 4-week urine culture is not mentioned in the publication.
- **Study Estebanezet al, 2009.** This study was conducted in Spain of the treatment of asymptomatic bacteriuria in pregnancy. Single 3g dose of oral fosfomycin was given in 18 patients in trimester 1, 17 patients in trimester 2, and 18 patients in trimester 3. Followup was throughout pregnancy and infants were examined at delivery. The results of the pregnancy outcomes and of the examination of the infants was not reported in the publication. Only one fosfomycin patient reported an adverse event (diarrhoea).
- **Study Ferreira et al, 2003.** In this open noncomparative study of the treatment of uncomplicated lower UTI in pregnancy with 3g single dose fosfomycin, 1021 of the 3446 patients were pregnant. 941 of these women reported a gestational age at treatment. Mean gestational age was 23.8 weeks with a median of 24.0 weeks, range was 2-40 weeks. Adverse events were nausea in 5.3% of patients, abdominal pain in 1.7% of cases and diarrhoea in 1.1% of cases. Presentation of adverse events was not stratified by pregnancy status and patients were not followed up beyond the day 7 urine culture. Hence pregnancy and infant outcomes were not reported.
- **Study Krcmery et al, 2001.** In this open-label study of the treatment of symptomatic UTI in pregnancy, 21 patients received single dose 3 g fosfomycin. Fosfomycin adverse events were

minor and transient, mostly nausea. Adverse event rate was not presented. Patients were followed to day 28-42 repeat urine culture only. Hence pregnancy and infant outcomes were not reported.

- **Study Usta et al, 2011.** In this open-label study of the treatment of symptomatic UTI at week 12 of gestation or later, 30 patients were treated with single dose 3g oral fosfomycin. Diarrhoea occurred in 10.7% of fosfomycin patients. Patients were followed to week 2 repeat urine culture only. Hence pregnancy and infant outcomes were not reported.
- **Study Zinner et al, 1990.** In this open-label study of the treatment of asymptomatic bacteriuria, gestational week or trimester of treatment was not specified. 153 patients were treated with single dose 3g oral fosfomycin. Patients were followed to day 25-30 repeat urine culture only. Hence pregnancy and infant outcomes were not reported.
- **Study Licciardello and Bignamini, contained in PSUR Jan 1995-Dec 1999.** This is a study of the treatment of asymptomatic bacteriuria in pregnancy with either single dose 3g fosfomycin or amoxicillin 500mg daily for 3 days. However, the publication included in the dossier is incomplete with all the figures omitted. It is also not clear how many patients received fosfomycin and the timing of the dose in relation to the pregnancy. It is important to review this paper particularly for safety in pregnancy. Could the sponsor provide the full paper in English please including all figures?

7.7.1.2. Safety in unexpected pregnancies in patients enrolled in the pivotal or main efficacy studies

The majority of the studies in the dossier excluded pregnant patients. However, two patients in the pivotal efficacy studies became pregnant, both 2 weeks after taking the dose. The offspring were followed to 15 and 24 months respectively and were developmentally normal. Three patients in the study by Krejci (1994) became pregnant at 4,6 and 8 months gestation respectively. Two were developmentally normal at birth and one was lost to followup. Details of the pregnancies are as follows:

- **Study US-MON-01.** One patient in Study US-MON-01 became pregnant 2 weeks after taking fosfomycin after birth control failed. She developed gestational diabetes and hypertension and delivered by Caesarian section one month prematurely. Her baby was examined 15 months after birth and had normal growth, development and physical examination.
- **Study US-MON-02.** One patient in Study US-MON-02 became pregnant 2 weeks after taking fosfomycin after birth control failed. She had an uncomplicated pregnancy and delivered a healthy child at term. The child was followed until the age of 24 months and had normal growth, development and physical examination.
- **Study Krejci, 1994.** Three patients in the study by Krejci became pregnant. Two patients who received fosfomycin at month 6 and month 8 of gestation, respectively, delivered healthy developmentally normal babies. The third pregnancy received fosfomycin at month 4 of gestation and was lost to follow-up.

7.7.1.3. Pregnant patients described in the PSURs

- **PSUR 1 Jan 2005 - 31 Aug 2009.** This reports 49 medically confirmed cases and 5 not medically confirmed cases of drug exposure during pregnancy recorded by Zambon Drug Safety Unit. It notes that 44 cases were those from the publication by Bayrak (2007) noted.
- **Data from all PSURs.** All PSURs contained in the dossier list 5 patients with adverse pregnancy outcomes. These are discussed in detail. All 5 regnancy adverse outcomes were for different conditions. None of the adverse pregnancy outcomes appear related to fosfomycin.

7.7.1.4. Listing of pregnancy outcomes and complications

Listed are 1 complicated abortion, 1 spontaneous abortion, 2 cases of neonatal jaundice, 1 stillbirth, and 9 congenital abnormalities from spontaneous and literature reports. The congenital abnormalities are one case each of as follows: congenital central nervous system abnormality, congenital pyelocaliectasis, hydrocele, macroglossia (2 cases), micrognathia, phalangeal agenesis, spina bifida and ventricular septal defect. No further details are provided but it is possible that some of these cases are those discussed from review of PSURs.

7.7.1.5. Prescription-event monitoring report, 1997

This report was an appendix attached to PSUR 1 Jan 1995 – 31 Dec 1999 and was conducted by the Drug Safety Research Trust, United Kingdom. It was a study of event reports sent to family practitioners who had treated patients with fosfomycin between February 1994 and June 1996. Pregnancy was reported as an event for 30 patients, information was available for 24 pregnancies. Thirteen mothers took fosfomycin during pregnancy, two during the first trimester.

There were 12 live births. One abnormality was reported, in this case a single dose of fosfomycin was taken by the mother in the third trimester of pregnancy, four days before delivery. The baby was born with congenital adrenal hyperplasia, a recessive condition due to a mutation or loss of the gene for 21-hydroxylase. The frequency of the defective gene is about 1 in 40, which gives a frequency of the disorder at about 1 in 7400 births. This case cannot be attributed to the use of fosfomycin as the drug was taken four days before delivery.

One further baby exposed to fosfomycin in the second trimester, was reported to have had a single short-lasting episode of apnoea when four days old. This baby also had a single febrile convulsion at just under one year of age. The general practitioner reported that this baby remained in good health with normal overall development.

There was one spontaneous abortion at approximately 19 weeks gestation. Sixteen conceptions occurred after the use of fosfomycin. One pregnancy was reported as unplanned, resulting in a therapeutic termination of pregnancy. In the remaining 15 cases it is unknown if the mothers were taking the combined oral contraceptive pill (OCP). In four cases the last menstruation occurred two to three weeks after taking fosfomycin. This study was unable to establish if any OCP failures took place as a result of taking fosfomycin.

Table 20: Pregnancies and fosfomycin prescription-event monitoring report, 1997 (Drug Safety Research Trust, UK)

Outcome:	TOTAL	Live birth	TOP	Ectopic pregnancy	Not Known	Spontaneous abortion
Drug stopped before pregnancy	16	4	3	0	6	3
Drug taken in 1st trimester	2	2	0	0	0	0
Drug taken 2nd/3rd trimester only	11	10	0	0	0	1
Exposure uncertain	1	0	0	1	0	0
TOTAL	30	16	3	1	6	4

7.7.2. Safety in lactation

7.7.2.1. Differences between proposed Australian PI and the PI from the United States regarding excretion into breastmilk and implications for safety

The dossier does not contain any information about safety in lactation apart from the single adverse event noted below. The 3 large pivotal studies and many of the other studies excluded nursing mothers. There is a concerning difference in the proposed Australian PI and the current PI from the United States regarding use in lactation. The proposed Australian PI states:

> *Use in lactation. Fosfomycin is excreted in breast milk. Monurol therapy should therefore not be used in breastfeeding mothers unless the potential benefit outweighs the potential risks.*

The PI from the United States (dated 2011) states:

> *Nursing Mothers. It is not known whether fosfomycin tromethamine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Monurol, a decision should be made whether to discontinue nursing or to not administer the drug, taking into account the importance of the drug to the mother.*

Comment: The dossier does not appear to contain any information about the excretion of fosfomycin into breast milk and this has potential implications for safety given the paucity of clinical studies in lactating mothers. Could the Sponsor please provide further information and / or human studies as to whether fosfomycin is excreted into breast milk? Is the comment based on studies in animals?

7.7.2.2. Adverse events during lactation

PSUR 1 Jan 2005 - 31 Aug 2009 p49 contains the following adverse event which could be related to fosfomycin. A breast-fed 1-month-old boy experienced persisting vomiting for five days. His mother took a single dose of MONURIL on the first day and nitrofurantoin from day 1-5, causality was assessed as unlikely to fosfomycin trometamol, being more probably related to nitrofurantoin.

Comment: Adverse event most likely related to nitrofurantoin rather than fosfomycin.

7.7.3. Safety in the elderly

There is limited data in the dossier regarding safety in the elderly. The single study of the treatment of UTIs in the elderly was by Ferraro et al (1990) and was a small open-label randomised study in elderly patients (defined as 50 years or older) with uncomplicated symptomatic lower UTI. Thirty patients received 3g single dose fosfomycin and 30 patients received norfloxacin 400 mg bd for 7 days. One fosfomycin and two norfloxacin patients had adverse events, all gastrointestinal intolerance.

Comment: Based on limited data, it is not anticipated that safety in the elderly with normal or mildly impaired renal function will be substantially different from safety in younger adult populations.

7.7.4. Safety in patients with hereditary abnormalities of sugar metabolism

7.7.4.1. Patients with fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency

This information is contained in PSUR Jan 2005-Aug 2009 PSUR p11. Zambon Nederland B.V in 2008 changed the safety warning in the PI. Information on sucrose content in the formulation has been updated with the following sentence: “This medicinal product contains sucrose. Patients with rare hereditary diseases as fructose intolerance, glucose-galactose malabsorption

or deficiency of sucrase-isomaltase should not use this product". This warning is also included in the proposed Australian PI.

Comment: Presumably this safety warning has been added because each sachet of Monurol contains more than 2g sucrose which patients with the hereditary deficiencies cannot metabolise. Is this the case? If so, what adverse events have been noted in these patients? Or is it a theoretical risk only? Does the sucrose load alter serum glucose levels in diabetes mellitus?

7.7.4.2. Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency

The pivotal study US-MON-01 excluded patients with G6PD deficiency. Presumably this is because the activity of fosfomycin is altered in the presence of glucose-6-phosphate. There is no other information presented regarding this possible secondary pharmacodynamic effects in the dossier and the implications of this for safety of the drug. Neither the proposed Australian PI or the current American PI lists G6PD deficiency as a precaution or a contraindication.

Comment: Is the Sponsor aware of any theoretical or actual secondary pharmacodynamic effects of fosfomycin in glucose-6-phosphate dehydrogenase deficient patients? Is this likely to alter safety in this patient population? Why was G6PD deficiency an exclusion criterion in the study US-MON-03?

7.7.5. Safety in other special populations

The dossier does not contain data on safety in other special populations.

7.7.6. Safety related to drug-drug interactions and other interactions

Five cases of decreased or increased INR are noted in the PSURs contained in the dossier but there are no details of whether these patients were taking warfarin. No other data contained in the dossier.

Comment: Fosfomycin has no serum protein binding and does not undergo metabolism so few drug-drug interactions occur and no safety issues are anticipated despite the lack of data.

7.7.7. Safety in overdose

Safety data in humans in overdosage is limited. One case was noted in a PSUR (1 Jan 1995 - 31 Dec 1999):

> *A patient took three 3g fosfomycin doses over a 6 day period and developed severe dizziness during therapy with vertigo and horizontal nystagmus. Bilateral vestibular loss was noted. The patient was referred to an otolaryngologist who noted symptom onset (mild) prior to fosfomycin. Vertigo was severe and lasted several months.*

This is not strictly overdosage when one considers the PK of the drug but is could be considered a supra-therapeutic dosage in a 72-year old with unknown renal function.

From the proposed PI, there appears to be some data in animal models which should have been reviewed by the nonclinical evaluator.

The proposed PI includes the following wording, under section "Overdose":

> *The following events have been observed in patients who have taken Monurol in overdose: vestibular loss, impaired hearing, metallic taste, and general decline in taste perception. In the event of overdosage, treatment should be symptomatic and supportive. Rehydration is recommended to promote urinary elimination of the drug.*

Comment: Based on the single case, the comment in the proposed PI appears appropriate although suggest nonclinical evaluator review comment as well after review of

animal model data. Could the Sponsor advise the source of the comments on taste alteration?

7.8. Evaluator's overall conclusions on clinical safety

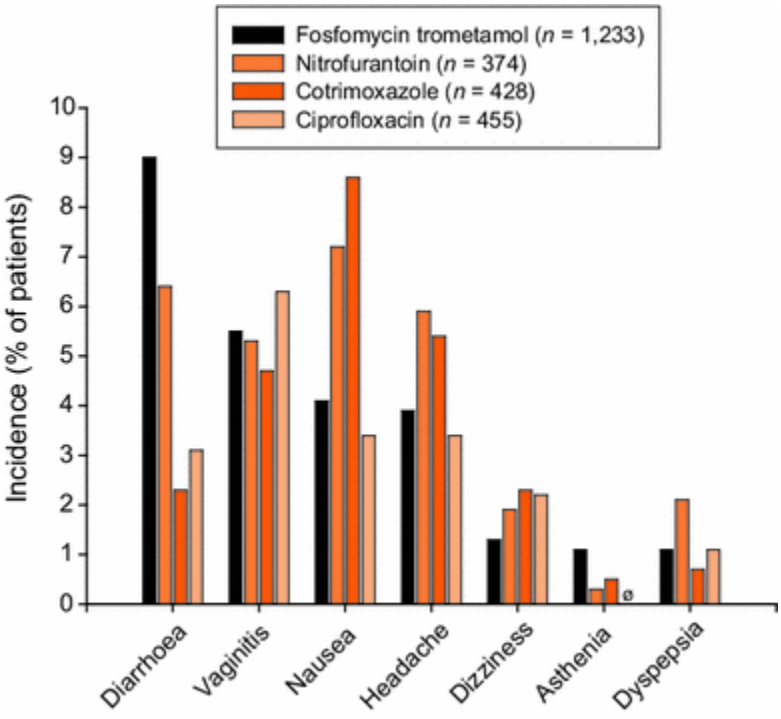
7.8.1. Clinical safety population and extent of exposure

- Three pivotal efficacy and safety studies conducted according to GCP with 1233 fosfomycin subjects evaluable for safety against 3 comparator antibiotics.
- Multiple non-pivotal efficacy and safety studies most predating GCP guidelines with 8668 fosfomycin subjects evaluable for safety.
- All patients in the pivotal studies were female. The majority of the patients in the other controlled and uncontrolled trials were female although some included males. The majority of patients were Caucasian.
- Most patients evaluable for safety had acute uncomplicated lower UTIs although some patients had chronic or recurrent UTIs or asymptomatic bacteruria.
- Pregnant patients and elderly patients were included in some trials.
- The vast majority of patients received a 3g dose of fosfomycin trometamol. A few adolescent females received a 2g sachet in countries where this dosing strength was available. It is likely they received a similar mg/kg dose by body weight compared to adult females.
- A few studies included patients dosed with more than one dose of fosfomycin. This was usually 3g daily for 3 doses. Insufficient patients received more than one dose of fosfomycin to be able to make any recommendations or safety analysis for multiple doses.

7.8.2. Common adverse events

- All 3 pivotal studies utilised the same 3g single fosfomycin trometamol dosage and were of similar study design, hence pooled data for drug-related adverse events, i.e adverse drug reactions across the 3 studies is shown. Comparator antibiotics were appropriately chosen and were nitrofurantoin 100 mg bd for 7 days (US-MON-03), TMP/SMX 1 DS tablet bd for 10 days (US-MON-02) and ciprofloxacin 250 mg bd for 7 days (US-MON-01). Note discussion of the incidence in the next few paragraphs is for all adverse events rather than drug-related adverse events, so percentages on the bar graph and in the following discussions are not the same.

Figure 7: Tolerability of fosfomycin trometamol 3g single dose in pooled data from the 3 pivotal efficacy and safety trials US-MON-01, US-MON-02 and US-MON-03.



* Shown are drug-related adverse events occurring in >1% of fosfomycin recipients. From Keating (2013) with original data from US prescribing information (FDA, 2011).

- The most commonly reported adverse event across the 3 pivotal studies was headache which was reported in 8.8-11.3% of fosfomycin patients. However in none of the studies was the rate significantly different in the comparator arm.
- The second most common adverse event across the 3 pivotal studies was diarrhoea which was reported in 7.6-14.7% of fosfomycin patients. In all 3 studies, this was a significantly higher incidence in the fosfomycin group than in the comparator arm (4.3% ciprofloxacin; p=0.04; 2.6% TMP/SMX, p<0.01; 8% nitrofurantoin, p=0.005).
- The third most common adverse event across the 3 pivotal studies was nausea which was 4.9-6.7% for fosfomycin. In the TMP/SMX study, TMP/SMX patients had a significantly higher rate of nausea 10%, p<0.01). For the other 2 comparators, there were no significant differences in rates of nausea.
- There were no significant differences between fosfomycin and the comparator antibiotics in the next most common adverse reactions, vaginitis, dizziness, asthenia, dyspepsia.
- The incidence of rash was low in the fosfomycin groups at 0.7-2.3%. Significantly more TMP/SMX patients developed rash (5.1%, p<0.01).
- Although diarrhoea is the most common adverse event, vomiting occurred in 0.9% and abdominal pain 1.9% of fosfomycin patients across the 3 studies.
- In the non-pivotal efficacy and safety studies (many of which were open-label), the most common fosfomycin adverse reaction was diarrhoea with incidence typically 5-10%. Other common adverse events in the fosfomycin arms of these studies were headache, nausea, rash and abdominal pain.

- In the meta-analysis by Falagas[27] of patients with uncomplicated UTIs treated with either single dose 3g fosfomycin (adults) versus single or multiple doses of comparator antibiotics, no difference was observed regarding the occurrence of adverse events in non-pregnant female patients treated with fosfomycin versus those treated with comparator(s) (13 RCTs, 2388 patients, RR=1.25, 95% CI=0.83–1.88).

7.8.3. Deaths and other serious adverse events

- There were no deaths in any of the clinical trials contained in the dossier.
- Serious adverse events were reported in 0.4%-5% of fosfomycin patients in the 3 pivotal studies, most commonly gastrointestinal intolerance. Rates of SAEs were not significantly different in the comparator arms. One fosfomycin patient developed an optic neuritis which resolved after steroid therapy.
- In the nonpivotal efficacy studies (many of which were open-label), SAEs in the fosfomycin arms was <1%. This was always due to gastointestinal intolerance, usually diarrhoea.

7.8.4. Discontinuations due to adverse events

- In the 3 pivotal studies, 20 (1.4-1.9%) of fosfomycin patients discontinued due to adverse events. Common causes were diarrhoea (n=9) and rash (3). Significantly more TMP/SMX patients discontinued due to rash and nitrofurantoin patients due to dizziness.
- Most of the nonpivotal studies did not report discontinuations separately from serious adverse events.

7.8.5. Post marketing experience

- Fosfomycin was first approved in 1986 (Italy) and is now authorised in more than 80 EU and non-EU countries. There is a large amount of usage and post-marketing experience with the drug worldwide. For example, from 1 August 2015 to 31 January 2016, a total of 9,015,221 packages (283,207 packages of 2 g sachets and 8,732,014 packages of 3 g sachets) were sold by Zambon affiliates and contractual partners worldwide.
- Nine Periodic Safety Update Reports (PSURs) conducted by the drug company Zambon are included in the dossier. They cover a continuous period from 1 January 1995 to 31 January 2016.
- Most safety issues with potential regulatory importance (discussed in the next section) have been identified from post marketing experience.

7.8.6. Safety issues of potential regulatory importance

- Fosfomycin has a number of rare adverse events of potential regulatory importance. The most important of these are likely to be immediate hypersensitivity, hepatitis, vestibular disturbance and deafness, and severe rash.
- **Immediate hypersensitivity (anaphylaxis, angiooedema, urticaria and asthma-like reactions)** Fosfomycin is clearly associated with immediate hypersensitivity in the form of anaphylaxis, angiooedema, urticaria and asthma-like reactions. These are well-described but appear rare from the data contained in the dossier. There were 7 reports of anaphylactic shock and/ or hypotension following fosfomycin in the PSURs. Onset after dosing was usually not specified but one case occurred 5 minutes after IV fosfomycin, one case started 10 minutes after an oral dosage and another case 30 minutes after an oral dosage. Three cases of Quincke's oedema were noted and 6 cases of facial or lip oedema. There were also cases or urticaria, cyanosis and dyspnoea.

[27] Falagas ME, et al. Fosfomycin. Clin Microbiol Rev. 2016 Apr;29(2):321-47.

- **Hepatitis.** Mildly abnormal liver function tests without symptoms which resolve are not uncommon. Clinical hepatitis, according to the information contained in the dossier, is rare. Twelve patients with hepatitis are recorded in the PSURs. Hepatitis in the 12 cases typically occurs 1-7 days after the dose. Hepatitis cases in the PSURs were mostly acute and sometimes associated with jaundice. Some cases were cholestatic. Most cases were reported to resolve although that information was not uniformly recorded. There was one case of fatal hepatitis necrosis in a 38 year old female. No details of her clinical history are available except that it occurred 7 days after single dose of fosfomycin for UTI. No information was available for concomitant medications for the fatal case.
- **Serious skin reactions.** From the data contained in the dossier, fosfomycin is associated with serious skin reactions but these are rare. There were 3 cases of toxic skin eruptions noted in the PSURs.
- **Vestibular disturbance and deafness.** Fosfomycin has been associated with deafness, tinnitus, and vestibular disorder but these adverse events appear rare. The PSURs contain one report of vertigo, vestibular loss and horizontal nystagmus lasting several months. There was another case of non-serious vertigo. There were 2 cases of reversible hearing loss. There was another report of reversible hearing loss in a patient taking fosfomycin every 15 days over a 2-year period (for an off-label indication). In overdosage, one case of vestibular disturbance has been described.
- **Severe gastrointestinal disturbance and / or *Clostridium difficile* colitis.** Despite the frequent occurrence of diarrhoea, severe diarrhoea requiring hospitalisation is rare. In most patients, diarrhoea resolves 1-7 days after the dose. *Clostridium difficile* colitis has been reported but is also rare, perhaps due to the drug's relatively small impact on normal bowel flora (see Pharmacodynamics section).
- **Haematological toxicity.** Fosfomycin has been associated with a range of haematological toxicities but all appear to be rare. The most common of the rare toxicities are mild anaemia, eosinophilia, thrombocytopenia, neutropenia and panyctopenia.
- **Cardiovascular toxicity.** Electrocardigraph monitoring was not performed during the clinical trials of fosfomycin. No QT/QTc studies were submitted. Based on the postmarketing data, the drug does not appear to be associated with significant cardiac toxicity.
- **Renal toxicity.** Based on the information contained in the dossier, fosfomycin does not appear to be have a significant association with renal toxicity. As the most common adverse reaction of fosfomycin is gastrointestinal intolerance, prerenal failure due to dehydration could occur.

7.8.7. Safety in pregnancy

- Fosfomycin crosses the placenta with high resultant high levels in the fetus soon after maternal dosing.
- The dossier contains nine clinical studies in which at least 1387 pregnant patients with either symptomatic lower UTI or asymptomatic bacteruria were treated with fosfomycin, usually 3g single dose. All of the studies were open-label and they were mostly small but they are important for consideration of safety of fosfomycin in pregnancy. Gestational age at treatment was not always specified but only two studies appear to include patients in the first trimester. Examination of offspring at birth or followup of the baby after birth was not commonly reported. In these studies, fosfomycin was generally well-tolerated in pregnancy and no adverse maternal or fetal outcomes were noted although the limited follow-up is noted.

- In the pivotal and main efficacy studies, 5 patients became unexpectedly pregnant. One patient was lost to follow up. Three patients had good maternal and fetal outcomes and one had early delivery for unrelated reasons.
- All PSURs contained in the dossier list only 5 patients with adverse pregnancy outcomes. All 5 pregnancy adverse outcomes were for different conditions. None of the adverse pregnancy outcomes appear related to fosfomycin.
- In a survey of family practitioners in the UK between February 1994 and June 1996, 30 patients treated with fosfomycin became pregnant with information available for 24 pregnancies. Thirteen mothers took fosfomycin during pregnancy, two during the first trimester. Sixteen conceptions occurred after the use of fosfomycin. There were 12 live births. Two abnormalities were reported, the first a case of congenital adrenal hyperplasia with delivery at term 4 days after fosfomycin dosing. After fosfomycin dosing in the 2nd trimester, the other baby had an apnoeic episode at day 4 and a febrile convulsion at just under one year of age. None of the abnormalities appear related to fosfomycin. There was one spontaneous abortion at approximately 19 weeks gestation and an unplanned pregnancy resulting in a therapeutic termination.
- At least 1400 women have received fosfomycin during pregnancy, usually 3g single oral dose. There is no evidence based on review of the human data that fosfomycin is associated with adverse fetal or maternal outcomes or teratogenicity.

7.8.8. Safety in lactation

- The dossier does not contain any information about safety in lactation. The 3 large pivotal studies and many of the other studies excluded nursing mothers.
- It is noted that proposed Australian PI states that fosfomycin is excreted in breast milk. However, the PI from the United States (dated 2011) states that it is not known whether fosfomycin tromethamine is excreted in human milk. Could the Sponsor please provide further information and / or human studies as to whether fosfomycin is excreted into breast milk? Is the comment based on studies in animals?

7.8.9. Safety in the elderly

- Based on limited data, it is anticipated that safety in the elderly with normal or mildly impaired renal function will not be substantially different from safety in younger adult populations.

7.8.10. Safety in patients with hereditary abnormalities of sugar metabolism

- The proposed Australian PI and foreign PIs state that “This medicinal product contains sucrose. Patients with rare hereditary diseases as fructose intolerance, glucose-galactose malabsorption or deficiency of sucrase-isomaltase should not use this product”. Presumably this safety warning has been added because each sachet contains more than 2g sucrose which patients with these hereditary deficiencies cannot metabolise. Is this the case? If so, what adverse events have been noted in these patients? Or is it a theoretical risk only? Does the sucrose load alter serum glucose levels in diabetes mellitus?
- The pivotal study US-MON-03 excluded patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Presumably this is because the activity of fosfomycin is altered in the presence of glucose-6-phosphate (see Mechanism of Action). Neither the proposed Australian PI or the current American PI lists G6PD deficiency as a precaution or a contraindication. Is the Sponsor aware of any safety issues in this patient population? Why was G6PD deficiency an exclusion criterion in the study US-MON-03?

7.8.11. Safety in overdose

- Safety data in humans in overdosage is limited. One case was noted in a PSUR of vestibular disturbance after a supratherapeutic dose. From the proposed PI, there appears to be some data on overdose and safety in animal models which should have been reviewed by the nonclinical evaluator.
- The proposed PI includes the following wording, under section "Overdose": "The following events have been observed in patients who have taken Monurol in overdose: vestibular loss, impaired hearing, metallic taste, and general decline in taste perception. In the event of overdosage, treatment should be symptomatic and supportive. Rehydration is recommended to promote urinary elimination of the drug. " What data are the taste disturbances based on?

7.8.12. Evaluator's overall conclusions on safety

- There is a large amount of safety data for fosfomycin trometamol available from clinical trials in humans and post-marketing experience. The drug has been available in many countries since the 1980s and 1990s.
- The majority of the safety data is for a single 3g oral dosage of fosfomycin trometamol in the proposed Monurol formulation.
- At least 1400 women appear to have taken the drug during pregnancy, most commonly during the 2nd and 3rd trimesters. Based on this data, the drug does not appear to be associated with poor maternal or fetal outcomes or teratogeneicity.
- The most common adverse event occurring with fosfomycin is diarrhoea which usually lasts 1-3 days but can last out to 7 days. It occurs in approximately 10% of patients. This is ually mild to moderate but can be severe.
- Other less common adverse events are headache, nausea, rash, vomiting, lethargy. The incidence of these adverse events appears to same or lower than common comparator antibiotics such as TMP/SMX, nitrofurantoin and ciprofloxacin.
- Serious but rare adverse events including anaphylaxis and other immediate hypersensitivity reactions. This appears much less common than for the beta-lactam class of antibiotics. Other rare serious adverse events include hepatitis, serious skin reactions, vestibular disturbance and deafness and haematological toxicity.
- There were no deaths in any of the clinical studies.

7.8.13. Limitations of safety studies

- Human safety data in the first trimester of pregnancy is limited.
- Human safety data in lactation is limited or non-existent.
- Safety data in populations apart from Caucasians and African-Amercians and in males is limited.
- Safety data for other dosages apart from a single 3g oral fosfomycin trometamol dosage is limited.
- Safety data in some special populations such as hepatic impairment is limited.
- The development of the drug predated mandatory electrocardiograph monitoring or QT/QTc studies in clinical trials. However, a large amount of post marketing experience would suggest that the drug is not associated with significant cardiotoxicity.

7.8.14. Questions on safety studies

- In pivotal study Mon-US-03, eosinophilia is reported in 57/362 (15.7%) of fosfomycin patients and 58/346 (16.8%) of nitrofurantoin patients (US-MON-03 report in the dossier). These are extraordinarily high results for both drugs. However, on review of the specific listing for eosinophilia, 20 (5.3%) fosfomycin patients and 14 (3.7%) nitrofuranotin patients appear to have had eosinophilia. This is still higher and out of keeping with studies MON-US-01 and Mon-US-02 in which eosinophilia rates were <1%. Could the Sponsor please advise the correct rates for eosinophilia for both study drugs? If the rates are till much higher than for fosfomycin in MON-US-01 and MON-US-02, could the Sponsor explain why? Was the formulation changed? Was any eosinophilia clinically significant?
- Is the warning in the Product Information about patients with rare hereditary diseases such as fructose intolerance, glucose-galactose malabsorption or deficiency of sucrase-isomaltase not using Monurol due to their inability to metabolise the sucrose in the product? If so, what adverse events have been noted in these patients? Or is it a theoretical risk only? Does the sucrose load alter serum glucose levels in diabetes mellitus?
- Is this the case? If so, what adverse events have been noted in these patients? Or is it a theoretical risk only? Does the sucrose load alter serum glucose levels in diabetes mellitus?
- Is the Sponsor aware of any safety issues in patients with hereditary abnormalities of sugar metabolism or G6PD deficiency?
- The proposed PI includes the following wording, under section “Overdose”: “The following events have been observed in patients who have taken Monurol in overdose: vestibular loss, impaired hearing, metallic taste, and general decline in taste perception. In the event of overdosage, treatment should be symptomatic and supportive. Rehydration is recommended to promote urinary elimination of the drug.” Could the Sponsor advise the source of the comments on taste alteration?

8. First round benefit-risk assessment

If multiple indications are proposed for the product, each indication should be supported by a separate benefit-risk analysis, with a separate heading.

8.1. First round assessment of benefits

8.1.1. Proposed indication 1: Treatment of acute uncomplicated lower urinary tract infections in women above 12 years of age

The benefits of fosfomycin trometamol (Monurol) in the proposed indication are:

- In non-pregnant adult and adolescent females, Monurol is an efficacious single 3g dosage treatment for acute lower uncomplicated UTI.
- The bacteriological efficacy rate of Monurol was 83-89% in three pivotal efficacy and safety trials performed in the USA in the 1990s. These suggest that 3g single dose Monurol has similar efficacy to 7 days of nitrofurantoin (100 mg twice-daily), but that it is is less effective than a 7-day oral regimen of ciprofloxacin (250 mg twice-daily) or a 10-day oral regimen of TMP/SMX (160 mg/800 mg tablet twice-daily). The three pivotal trials had some issues of design discussed below in "Strengths and uncertainties of the evidence".
- Evidence from multiple nonpivotal trials supports the bacteriological efficacy rate of 83-89% found in the pivotal studies.

- Fosfomycin has good efficacy against *E coli*, which causes 70-95% of acute uncomplicated lower UTIs in adult and adolescent females.
- Fosfomycin is generally efficacious against other less common uropathogens in females such as *Proteus* and *Klebsiella* and has variable activity against other Gram negative uropathogens and *Staph saphrophyticus.*
- A single 3g oral dosage has favourable pharmacokinetics and is likely to improve patient compliance compared to multiple-daily dosing of other antibiotics.
- Fosfomycin has a favourable safety profile and was well-tolerated in the pivotal and nonpivotal trials. Diarrhoea was the most common adverse reaction occurring in approximately 10% of patients. This usually resolves within 1-3 days and was usually mild to moderate. Nausea, vomiting and abdominal pain occurred in <5% of patients and were usually mild.
- Fosfomycin was better tolerated than TMP/SMX in a pivotal study and had similar tolerability in another pivotal study to nitrofurantoin.
- There is a large post-marketing experience with fosfomycin. Most severe adverse reactions, are rare. The most common of these are immediate hypersensitivity and hepatitis. Severe ADRs are not common enough to cause concern in the approval process.

The strengths and uncertainties of the evidence are:

- The first 2 pivotal studies MON-US-01 and MON-US-02 incorrectly classified patients receiving concomitant antibiotics as discontinuations rather than treatment failures for the purposes of the efficacy analysis. There were no significant differences in concomitant antibiotic use in the two treatment groups of Study MON-US-02 but in the Study MON-US-01, 25% of fosfomycin patients used concomitant antibiotics compared to 13% in Study MON-US-01 ($p<0.01$). This likely overestimated the efficacy rates for fosfomycin and the comparator antibiotics. In the later Study MON-US-03, efficacy variables were correctly assigned and the bacteriological efficacy of fosfomycin was 83%.
- There are no good pivotal trials comparing Monurol to trimethoprim or cephalexin, which are the recommended 1st or 2nd line therapy of acute uncomplicated lower UTIs in Australia (Therapeutic Guidelines Antibiotic 2014).
- More than 1000 pregnant patients have been treated without any evidence of poor maternal or fetal outcomes or teratogenicity in humans. However, single dose therapy of UTIs is not recommended in international guidelines due to lower efficacy rates compared to multiple-day regimens. If pregnant patients receive fosfomycin single dose, it would be important to check post-treatment that bacteriological eradiction has occurred by urine culture.
- The drug has been sufficiently studied in immunocompetent adult and adolescent females with acute uncomplicated lower UTI.
- There is a potential for off-label usage in the treatment of ESBL-producing and carbapenemase-producing Gram negative lower UTIs. The current SAS usage of the drug is usually in patients with uncomplicated or complicated lower UTis caused by these organisms. This is in fact a potential benefit of approval of the drug in Australia. However, the dosing schedule of fosfomycin has not been properly studied in the treatment of complicated UTI or in patients who are immunocompromised such as renal transplant patients.

8.1.2. Proposed indication 2: Prophylaxis of urinary tract infections in surgical and diagnostic procedures involving the lower urinary tract in adult males and females

- The major current Australian and international indication for antibiotic prophylaxis in surgical or diagnostic procedures involving the urinary tract is in the surgical prophylaxis of TURP and transurethral prostatic biopsy. Antibiotic prophylaxis is generally not indicated in minor urological procedures such as cystoscopy or ureteroscopy. The wording of the proposed indication is extremely general and would include many patients who do not require antibiotic prophylaxis.

The strengths and uncertainties of the evidence are:

- There were no good quality studies in the dossier comparing fosfomycin to another appropriate antibiotic in the prophylaxis of TURP or transurethral prostatic biopsy.
- In the prophylaxis of TURP, two relatively poor quality studies compared fosfomycin either to placebo or to a poor choice of comparator.
- In the other two surgical prophylaxis studies included in the dossier, most of the patients in these studies did not require surgical antibiotic prophylaxis as they underwent minor urological procedures only.
- Efficacy studies contained in the dossier are of insufficient content and insufficient quality to approve this proposed indication.

8.2. First round assessment of risks

8.2.1. Proposed indication 1: Treatment of acute uncomplicated lower urinary tract infections in women above 12 years of age

The risks of Monurol in the proposed usage are:

- As yet unidentified ADRs. However the large postmarketing experience in other countries for over 30 years makes this unlikely.
- As yet unidentified drug interactions. In humans, data was only available for cimetidine and metoclopramide.
- No data is available in patients with hepatic impairment.
- No data is available in peritoneal dialysis or haemofiltration. Data in haemodialysis patients or significant renal impairment is very limited.
- Little or no data in lactating patients.
- No data is available in immunocompromised patients.
- Limited data in racial groups other than Caucasian or African-American.
- The dosing schedule in patients with complicated acute lower UTI is unknown.
- The dosing schedule in male patients with UTI is unknown.
- There is no data for patients with pyelonephritis so the drug should not be used to treat patients with upper UTI or bacteremia.
- The drug has limited and variable efficacy in the treatment of acute uncomplicated UTI caused by *Staphylococcus saphrophyticus.* This organism is usually the 2-4th most common uropathogen in adult and adolescent females and is more common in a community than a hospital setting. It is most common in young sexually active females and, as the cause of "honeymoon cystitis", it is a marker of onset and frequency of sexual activity.

- Susceptibility testing for fosfomycin is currently limited in Australia. However, this is likely to change if the drug is approved and there are no barriers to the occurrence of this.
- In 1997, soon after approval of fosfomycin in the United States, the drug was substantially more expensive than other common multiple-day antibiotic courses for acute lower UTI (Fosfomycin for urinary tract infections 1997). This may occur in Australia as well. It is noted that short courses of the first-line UTI agents (trimethoprim or cephalexin) are relatively inexpensive.
- The draft RMP Appendix "Fosfomycin trometamol Australian post-marketing surveillance proposal) refers to the drug being used as a first-line agent for the treatment of acute uncomplicated UTIs in Australia. In the United States, fosfomycin is not recommended for first-line therapy due to lower efficacy compared to comparator antibiotics. In my opinion, fosfomycin should not be a first-line antibiotic for acute uncomplicated UTI treatment in Australia for reasons of lower efficacy and possibly higher cost. However, it could be a useful third-line agent or fourth-line agent or even a second-line agent, especially where resistance has occurred to first-line agents, allergies or in patients in whom compliance could be be an issue (due to single dose).[28]
- The development of fosfomycin resistance as a possible result of therapy has been identified by the Sponsor in the draft RMP as a key consideration. However, the Sponsor has not provided sufficient material in the dossier in this area. Consideration of this issue is key to the approval process of any antimicrobial agent. The review paper in this area contained 53 references only 5 of which have been provided in the submission. The 5 publications provided are generally old and out of date. The missing resistance studies require review by the TGA and the Sponsor is requested to provide these by round 2 of the approval process.

8.2.2. Proposed indication 2: Prophylaxis of urinary tract infections in surgical and diagnostic procedures involving the lower urinary tract in adult males and females

- The dossier contains insufficient evidence to support this proposed indication.
- Fosfomycin has good prostatic penetration so the Sponsor is encouraged to perform good quality prophylaxis studies for single dose fosfomycin 3g against an appropriate comparator. These comparators might include single dose gentamicin for TURP prophyalxis or single dose oral ciprofloxacin for transrectal prostate biopsy prophylaxis.

8.3. First round assessment of benefit-risk balance

8.3.1. Proposed indication 1: Treatment of acute uncomplicated lower urinary tract infections in women above 12 years of age

- The benefit-risk balance of Monurol is unfavourable for the proposed usage, but could become favourable if the changes and additional information recommended are adopted.

8.3.2. Proposed indication 2: Prophylaxis of urinary tract infections in surgical and diagnostic procedures involving the lower urinary tract in adult males and females

- The benefit-risk balance of Monurol for the proposed usage is unfavourable.

[28] Please also refer to the second round assessment, Question 12.3.5. TGA Question 5, clarifying that the three recommended first-line therapies for acute uncomplicated lower UTI in the USA are fosfomycin, trimethoprim/sulphamethoxazole and nitrofurantoin. See below for further details

9. First round recommendation regarding authorisation

9.1. Proposed indication 1

"Treatment of acute uncomplicated lower urinary tract infections in women above 12 years of age"

- Approval is not recommended for the proposed indication at this time. The sponsor is requested to respond to the clinical questions and to provide all relevant studies in the area of fosfomycin resistance development for consideration by the TGA at the second round.
- Efficacy: Fosfomycin resistance development has the potential to compromise efficacy. The Sponsor is asked to provide all relevant studies in the area of fosfomycin resistance development for consideration by the TGA at the second round. Otherwise, sufficient has been provided for efficacy, subject to adequate response to clinical questions.
- Safety: Sufficient data provided subject to adequate response to clinical questions.

9.2. Proposed indication 2

"Prophylaxis of urinary tract infections in surgical and diagnostic procedures involving the lower urinary tract in adult males and females"

- Approval is not recommended for the proposed indication. There is insufficient efficacy data at the present time for the proposed indication.

10. Clinical questions

10.1. Additional expert input

10.1.1. Review by a biostatistician

Recommend review of some statistical methods in pivotal studies MON-US-01 and MON-US-02 by a biostatistician. Specifically, these studies changed from a one-tailed to a two-tailed 0.05 level of significance during the course of the study. Recommend that a biostatistician be consulted as to the impact if any of this change to the study. Also, all 3 pivotal studies used a critical p-value of 0.05 for declaring statistical significance. Although p values were provided for all efficacy outcomes, confidence intervals were rarely provided. Confidence intervals were only provided for bacteriological efficacy. Does the biostatistician consider the statistical interpretation of efficacy outcomes is compromised by this (taking into account the studies were conducted during the 1990s).

10.1.2. Consultation between clinical evaluator and nonclinical evaluator

A review of nonclinical Table of Contents suggests that the Sponsor has submitted few if any publications on resistance development and in particular of mechanisms of resistance development and ease of resistance occurring. If the nonclinical evaluator has not identified and reviewed the missing data, this will need to be done as a critical part of this evaluation. It is recommended that the nonclinical and clinical evaluators consult on this issue as required.

10.2. Pharmacokinetics

Question 1

Could the Sponsor please provide further information (animal or human data) regarding the distribution of fosfomycin into breast milk? Note the differences between the proposed Australian data which states that the drug is distributed into breastmilk and the PI in the USA stating that it is unknown whether the drug is excreted into breastmilk.

Question 2

Could the Sponsor please provide the full poster or publication by Chezzi (1989) regarding the penetration of fosfomycin into seminal vesicles? The abstract of this poster in the dossier does not contain sufficient information.

Question 3

Is the Sponsor aware of any PK data in peritoneal dialysis or haemofiltration?

Question 4

Could the Sponsor provide more data regarding the biliary excretion and enterohepatic circulation of drug, specifically the publications referred to in the paper by Segre (1987) contained in the dossier?

Question 5

Is the Sponsor aware of any other studies regarding PK drug interactions? Why do some of the early publications refer to possible fosfomycin interactions for lithium or balsalazide? Could the Sponsor provide these studies? if not, could the Sponsor comment on whether there is a potential interaction between lithium or balsalazide with fosfomycin?

Question 6

Fosfomycin accumulates in patients with renal impairment, however the clinical significance of this appears to be unknown. The last sentence in the publication by Fillastre (1988) recommends dosage reduction in patients with chronic renal sufficiency, however this has not been recommended in the proposed PI. Could the Sponsor comment further? Is the Sponsor aware of any data regarding the accumulation of the drug in patients with renal failure and any negative potential consequences of this?

10.3. Pharmacodynamics

Question 1

Is the Sponsor aware of any theoretical or actual secondary pharmacodynamic effects of fosfomycin in glucose-6-phosphate dehydrogenase deficient patients? Why was G6PD deficiency an exclusion criterion in the study US-MON-03?

Question 2

The Sponsor has not included any studies of fosfomycin resistance development and mechanisms from 1994 onwards. At least 13 studies were identified easily from two review papers contained. These studies are the references in the paper by Keating (Karageorgopoulos et al, 2012; Marchese et al, 2003; Nilsson et al, 2003; Oteo et al, 2009; Rodriguez-Avial et al, 2013; Oteo et al, 2010) and the references in the paper by Michalopoulos (2011) (Beharry et al, 2005; Horii et al, 1999; Garcia et al, 1994; Cao et al, 2001; Bernat et al, 1997; Rigsby et al, 2005; Arca et al, 1997). There are also 48 studies referred to in the review paper on fosfomycin resistance. The lack of recent studies on resistance mechanisms and development is a serious omission from the dossier. Has the Sponsor taken care to update the dossier and ensure it is current since approval of fosfomycin by the FDA in 1996 and Canada in 1999? A current review of resistance development and mechanisms is critical to the approval process of any antimicrobial agents. Please ask the Sponsor to provide the studies above and any other relevant studies published in the last 20 years for review by the reviewer, as appropriate.

Question 3

Could the Sponsor provide the recent studies on mutant selection windows and mutant prevention concentrations for review to the evaluator, as appropriate (if not already reviewed by the evaluator)? The studies are Mei Q, Ye Y, Zhu YL, et al. Eur J Clin Microbiol Infect Dis. 2015 Apr;34(4):737-44 ; Liu LG, Zhu YL, Hu LF, et al. J Antibiot (Tokyo). 2013 Dec;66(12):709-12; and the unpublished study if results are available referred to in PSUR1 Aug 2015-31 Jan 2016.

10.4. Efficacy

Question 1

The placebo sachet in pivotal studies US-MON-01, US-MON-02 and US-MON-03 was matched for appearance with the fosfomycin sachet. A mandarin and / or orange juice flavour plus sweetener was used. Was the placebo sachet also matched for taste?

Question 2

In pivotal studies MON-US-01 and MON-US-02, why was it considered necessary to change from a one-tailed to a two-tailed 0.05 level of significance?

Question 3

In study MON-US-01, recurrence rates for fosfomycin were higher than for ciprofloxacin. Could the Sponsor provide the results of the susceptibility testing for ciprofloxacin and fosfomycin for the recurrent isolates? Did the recurrent isolates develop resistance to the study drug?

Question 4

For study MON-US-02, could the Sponsor provide the results of the susceptibility testing for fosfomycin and TMP/SMX for the recurrent isolates? Did the recurrent isolates develop resistance to the study drug?

Question 5

In Studies MON-US-01, MON-US-02 and MON-US-03, are p values available for the comparison between the comparator antibiotic and fosfomycin for bacteriological efficacy against *E coli*?

Question 6

Study US-MON-03 contains the following information: “In its evaluation of the efficacy of FT in the MON-US-01 and MON-US-02 trials, the FDA presented results to an Advisory Committee based on criteria which differed in certain respects from those defined prospectively in the protocols. Primarily, the FDA included the use of antibiotics for UTI as a criterion for failure and data from patients with "missing" visits were handled either by excluding the patient from the modified ITT analysis (for non-completers who discontinued for reasons other than treatment failure or related reasons) or by assigning outcomes on a case-by-case basis (for non-completers who remained in the modified ITT population because their discontinuation reason was related to treatment failure)”.

Is the Sponsor able to provide the full transcript of the FDA report and also the statistical repeat analysis done according to the FDA recommendations?

Question 7

The 3 pivotal studies MON-US-01, MON-US-02 or MON-US-03 do not contain much data on antimicrobial susceptibility testing results after therapy and whether resistance development occurred to the study drug. There is some individual patient data in MON-US-03 but is difficult to tease out and appears incomplete. Of particular importance is MON-US-01 which showed a significantly higher recurrence rate for fosfomycin patients compared to ciprofloxacin patients

(14% versus 4%, p<0.01). Is the Sponsor able to provide any further antimicrobial resistance data for any of the 3 studies in early and late follow-up urine cultures after therapy?

Question 8

In PSUR Jan 1995-Dec 1999, the publication by Licciardello and Bignamini on the efficacy and safety of fosfomycin is missing all Figures. Could the Sponsor provide the full paper including all Figures please?

10.5. Safety

Question 1

In pivotal study Mon-US-03, eosinophilia is reported in 57/362 (15.7%) of fosfomycin patients and 58/346 (16.8%) of nitrofurantoin patients (US-MON-03 report in the dossier). These are extraordinarily high results for both drugs. However, on review of the specific listing for eosinophilia, 20 (5.3%) fosfomycin patients and 14 (3.7%) nitrofuranotin patients appear to have had eosinophilia. This is still higher and out of keeping with studies MON-US-01 and Mon-US-02 in which eosinophilia rates were <1%. Could the Sponsor please advise the correct rates for eosinophilia for both study drugs? If the rates are till much higher than for fosfomycin in MON-US-01 and MON-US-02, could the Sponsor explain why? Was the formulation changed? Was any eosinophilia clinically significant?

Question 2

This information is contained in PSUR Jan 2005-Aug 2009 PSUR p11. Zambon Nederland B.V in 2008 changed the safety warning in the PI. Information on sucrose content in the formulation has been updated with the following sentence: “This medicinal product contains sucrose. Patients with rare hereditary diseases as fructose intolerance, glucose-galactose malabsorption or deficiency of sucrase-isomaltase should not use this product”. This warning is also included in the proposed Australian PI. Presumably this safety warning has been added because each sachet of Monurol contains more than 2g sucrose which patients with the hereditary defiencies cannot metabolise. Is this the case? If so, what adverse events have been noted in these patients? Or is it a theoretical risk only? Does the sucrose load alter serum glucose levels in diabetes mellitus?

Question 3

Is the Sponsor aware of any safety issues in patients with hereditary abnormalities of sugar metabolism or G6PD deficiency?

Question 4

The proposed PI includes the following wording, under section “Overdose”: “The following events have been observed in patients who have taken Monurol in overdose: vestibular loss, impaired hearing, metallic taste, and general decline in taste perception. In the event of overdosage, treatment should be symptomatic and supportive. Rehydration is recommended to promote urinary elimination of the drug.” Could the Sponsor advise the source of the comments on taste alteration?

11. Second round evaluation of clinical data submitted in response to questions

The Sponsor has provided the responses to the Clinical Questions raised by the clinical evaluator after first round assessment. The Sponsor has provided 27 new references. The response contains two new review fosfomycin papers. The second round assessment includes new versions of the draft PI, draft CMI and draft RMP.

In addition, during the second round evaluation the clinical evaluator has read the nonclinical evaluator's first round assessment report which was provided by the TGA delegate. This contained some clinical questions raised by the nonclinical evaluator and allowed consideration of some areas of clinical and non-clinical overlap.

The Sponsor's 2nd proposed indication for prophylaxis of urinary tract infections in surgical and diagnostic procedures involving the lower urinary tract in adult males and females was not recommended at first round review. The Sponsor has accordingly removed this indication from the proposed Australian PI.

The second round evaluation henceforth specifically and only refers to the Sponsor's 1st proposed indication, treatment of acute uncomplicated lower urinary tract infections in women above 12 years of age.

In this section, the TGA question is followed by the sponsor's response to the query and then the evaluator's comment on the sponsor's response.

11.1. Pharmacokinetics

11.1.1. TGA Question 1

- Could the Sponsor please provide further information (animal or human data) regarding the distribution of fosfomycin into breast milk? Note the differences between the proposed Australian data which states that the drug is distributed into breastmilk and the PI in the USA stating that it is unknown whether the drug is excreted into breastmilk.

Sponsor's response

A few data on the excretion of the fosfomycin trometamol in milk are described in the article published by Kirby (1977). The analysis performed after the parental administration of 1-2 g fosfomycin on two patients shows that fosfomycin is excreted into human milk at a low level after a single injection. In the two women, fosfomycin was excreted into collustrum and milk at concentrations that were 4.8 and 3.6 µg/ml, respectively. It is estimated that the breastfed infant would receive a daily dose of less than 1% of the maternal weight-adjusted dose of fosfomycin. Due to the limited amount of data available, the Sponsor wishes to maintain the current statement included in the Australian PI: “Use in lactation. Fosfomycin is excreted in breast milk. Monurol therapy should therefore not be used in breastfeeding mothers unless the potential benefit outweighs the potential risks.”

Evaluator's response

Based on very limited data (2 patients in the study by Kirby 1977), it appears that fosfomycin is excreted into breast milk and colustrum in small amounts. The evaluator is therefore satisfied with the sponsor's response and the sponsor's proposed wording for use in lactation in the Australian PI.

11.1.2. TGA Question 2

- Could the Sponsor please provide the full poster or publication by Chezzi (1989) regarding the penetration of fosfomycin into seminal vesicles? The abstract of this poster in the dossier does not contain sufficient information.

Sponsor's response

The Chezzi (1989) full publication (including English translation) is provided.

Evaluator's response

The sponsor has now provided the full publication in English translation. This study shows that fosfomycin has good penetration into seminal vesicles and prostate. Hence the statement in the

Distribution section of the Australian PI is factual and should stand: "Fosfomycin is distributed to the kidneys, bladder wall, prostate and seminal vesicles."

11.1.3. TGA Question 3

· Is the Sponsor aware of any PK data in peritoneal dialysis or haemofiltration?

Sponsor's response

Available data on PK in peritoneal dialysis and haemofiltration is very limited. In light of the above, the Sponsor accepts the proposal of the TGA to add a statement in the PI that PK data on patients in peritoneal dialysis and haemofiltration are limited, see annotated and clean Product Information (v 0.3).

Evaluator's response

There appears to be no data in peritoneal dialysis or haemofiltration. The PI should state that there is no data, rather than that data is limited. In the revised PI, the Sponsor has stated that the drug is contraindicated in haemodialysis. Based on the lack of data and the similarities to haemodialysis, the evaluator recommends that oral fosfomycin is contraindicated in peritoneal dialysis and haemofiltration as well.

11.1.4. TGA Question 4

· Could the Sponsor provide more data regarding the biliary excretion and enterohepatic circulation of drug, specifically the publications referred to in the paper by Segre (1987) contained in the dossier?

Sponsor's response

The publications included in the paper of Segre (1987) on enterohepatic recirculation are Shepard (1985) and Kirby (1977). The studies confirm that there is an enterohepatic recirculation without any influence on bioavailability. The Sponsor provides the two abovementioned studies.

Evaluator's response

In the study by Kirby (1977), in 4 patients with cholecystitis, concentrations in bile after IV administration were 20% of serum levels. This percentage is comparable to the study by Segre (1987) previously reviewed. The reference by Sheppard (1985) has no fosfomycin-specific data. The evaluator is satisfied with the sponsor's response.

Additionally, the study by Kirby (1977) newly provided by the Sponsor also shows that in 3 women, concentrations of fosfomycin in amniotic fluid and fetal blood are high after IV administration. There is no available human amniotic fluid or fetal data after oral administration but it would be expected that there would be no substantial differences between the oral or IV formulations. Also, according to the nonclinical evaluator, the drug is also known to cross the placenta in animals. Hence the statement in the Australian PI could be reworded to "....fosfomycin has been shown to cross the placental barrier in humans and animals." Falagas et al (Clin Micro Rev 2016) states "Fosfomycin is reported to cross the placental barrier through simple diffusion but does not affect the placental transport of other nutrients (208). Reference 208 is "Iioka H, Moriyama I, Kyuma M, Tsuji Y, Ichijo M. 1986. The transport mechanism of antibiotics using microvillous membrane vesicles (placental transport of fosfomycin). Nihon Sanka Fujinka Gakkai Zasshi 38: 1702–1706. "Could the sponsor provide an English translation of this paper for review to enable the clinical evaluator for review to decide on the specific wording of the placental transfer in humans in the PI?

11.1.5. TGA Question 5

· Is the Sponsor aware of any other studies regarding PK drug interactions? Why do some of the early publications refer to possible fosfomycin interactions for lithium or balsalazide?

Could the Sponsor provide these studies? If not, could the Sponsor comment on whether there is a potential interaction between lithium or balsalazide with fosfomycin?

Sponsor's response

The Sponsor, to the best of its knowledge, is not aware of any documentation on the interactions of fosfomycin with balsalazide and lithium. The UK SmPCs of these two medicinal products do not mention any interaction with fosfomycin either. Moreover, no drug-drug interaction cases describing interaction with balsalazide and lithium was received up to 31 July 2016 by Zambon S.p.A., holder of the marketing authorisation in several countries worldwide, during thep ostmarketing surveillance activity.

Evaluator's response

The evaluator is satisfied with the sponsor's response regarding balsalazide and lithium. The paper by Falagas et al (Clin Micro Rev 2016) included by the Sponsor in round 2 states:

> *Fosfomycin may increase the levels or effects of digoxin; patients should be monitored closely when digoxin and fosfomycin are coadminstered. A low risk for contraceptive failure exists when fosfomycin is coadministered with conjugated estrogens..... Finally, fosfomycin trometamol should not be coadministered with probenecid which decreases renal clearance and excretion of fosfomycin (Paladin Labs, 2007, Monurol package insert, Canada).*

Could the Sponsor please advise whether there are clinically significant interactions of fosfomycin with digoxin, conjugated estrogens and / or probenecid? If so, statements will need to be added to the Australian PI.

11.1.6. TGA Question 6

· Fosfomycin accumulates in patients with renal impairment, however the clinical significance of this appears to be unknown. The last sentence in the publication by Fillastre (1988) recommends dosage reduction in patients with chronic renal sufficiency, however this has not been recommended in the proposed PI. Could the Sponsor comment further? Is the Sponsor aware of any data regarding the accumulation of the drug in patients with renal failure and any negative potential consequences of this?

Sponsor's response

To the best of our knowledge, no additional data on patients with chronic renal insufficiency are available. Since fosfomycin is indicated as single-dose therapy, accumulation of the drug will not occur and therefore dose adjustment is likely to be unnecessary.

Evaluator's response

The evaluator is satisfied with the sponsor's response.

11.2. Pharmacodynamics

11.2.1. TGA Question 1

· Is the Sponsor aware of any theoretical or actual secondary pharmacodynamic effects of fosfomycin in glucose-6-phosphate dehydrogenase deficient patients? Why was G6PD deficiency an exclusion criterion in the study US-MON-03?

Sponsor's response

No data on pharmacodynamics effects of fosfomycyin in glucose-6-phosphate dehydrogenase deficient patients are available. A search of the Company's worldwide database of all cases that have been cumulatively collected up to 31 Dec 2016, did not reveal any case reporting as Medical History a condition mapping to SMQ Congenital, familial and genetic disorders and

describing hereditary abnormalities of sugar metabolism or G6PD deficiency. The study MON-US-03 is a double-blind double-dummy study, so the exclusion criteria is referred for both of the enrolled groups of patients but it is likely linked to only nitrofurantoin because there is a high risk safety concern for interaction between G6PD deficiency and nitrofurantoin.

Evaluator's response

The evaluator is satisfied with the sponsor's response.

11.2.2. TGA Question 2

- The Sponsor has not included any studies of fosfomycin resistance development and mechanisms from 1994 onwards. At least 13 studies were identified easily from two review papers contained. These studies are the references in the paper by Keating (Karageorgopoulos et al, 2012; Marchese et al, 2003; Nilsson et al, 2003; Oteo et al, 2009; Rodriguez-Avial et al, 2013; Oteo et al, 2010) and the references in the paper by Michalopoulos (2011) (Beharry et al, 2005; Horii et al, 1999; Garcia et al, 1994; Cao et al, 2001; Bernat et al, 1997; Rigsby et al, 2005; Arca et al, 1997). There are also 48 studies referred to in the review paper on fosfomycin resistance. The lack of recent studies on resistance mechanisms and development is a serious omission from the dossier. Has the Sponsor taken care to update the dossier and ensure it is current since approval of fosfomycin by the FDA in 1996 and Canada in 1999? A current review of resistance development and mechanisms is critical to the approval process of any antimicrobial agents. Please ask the Sponsor to provide the studies above and any other relevant studies published in the last 20 years for review by the reviewer, as appropriate.

Sponsor's response

In response to the above TGA request for recent studies on resistance mechanism and development, the Sponsor has subsequently clarified with the TGA via email on 13th February that recent publications up to Year 2015 (report and associated literature) are provided. Thereafter, on 20th February, TGA requested that the Sponsor supply the following references:

- Rodriguez-Avial 2013, from review paper by Keating;
- Beharry 2005, Horii 1999, Garcia 1994, Cao 2001, Bernat 1997, Rigsby 2005, Arca 1997, from review paper by Michalopoulos.

The requested references are included.

The Sponsor wishes to also refer to a written report by an expert which discusses the current empiric treatment of acute uncomplicated cystitis and the resistance rates in E.coli. (including multi-drug resistant (MDR) extended spectrum β-lactamase (ESBL) producing E.coli.). The report concludes that “Fosfomycin has been reported to demonstrate the lowest resistance of all oral agents with E.coli (<1%) including MDR ESBL E.coli (<1%).”

Furthermore, the sponsor has also provided a local commentary on the report from an Australian Infectious Disease Specialist. A copy of the local commentary and the report is provided.

Evaluator's response

The Resistance Risk Assessment is an area of overlap between the clinical and nonclinical evaluators. Hence, the clinical evaluator has reviewed the nonclinical evaluator's round 1 report. Additionally, the five new references provided at round 2 have been reviewed. The reports provided at round 2 have been reviewed, and the 14 references have also been reviewed. The evaluator has sufficient information and is satisfied with the sponsor's response.

11.2.3. TGA Question 3

- Could the Sponsor provide the recent studies on mutant selection windows and mutant prevention concentrations for review to the evaluator, as appropriate (if not already reviewed by the evaluator)? The studies are Mei Q, Ye Y, Zhu YL, et al. Eur J Clin Microbiol Infect Dis. 2015 Apr;34(4):737-44; Liu LG1, Zhu YL1, Hu LF1, et al. J Antibiot (Tokyo). 2013 Dec;66 (12):709-12; and the unpublished study if results are available referred to in PSUR1 Aug 2015-31 Jan 2016.

Sponsor's response

The published studies, Mei 2015, Liu 2013 and Novelli 2017 (the final report from the study "Evaluation of mutant prevention concentration (MPC) and mutant selection window (MSW) of fosfomycin trometamol against Gram-negative uropathogens in an in vitro dynamic model" [mentioned in PSUR 1 Aug 2015-31 Jan 2016]) are provided.

Evaluator's response

Novelli et al (2017) is of most interest as resistance development and mutant prevention concentrations (MPCs) are assessed in an in vitro PK model using Mueller Hinto broth for 4 clinical strains of common uropathogens (E coli including one ESBL-producing strains mirabilis and K pneumoniae). Fosfomycin had good bactericidal activity at simulated urinary concentrations of 1250-5000 mg/L. MPCs were 8-32x MIC. However at a lower simulated uranary concentration of 625 mg/L, fosfomycin was bactericidal but resistant mutants developed by 48h for 3 of the 4 strains, with MIC post-fosfomycin 8-16 times the original MIC. Biological fitness of resistant mutants were not assessed in this paper. Mei (2015) and Liu (2013) were of less clinical utility, as the bacteria tested (S aureus and S epidermidis) are not common uropathogens.

The evaluator is satisfied with the sponsor's response.

11.3. Efficacy

11.3.1. TGA Question 1

- The placebo sachet in pivotal studies US-MON-01, US-MON-02 and US-MON-03 was matched for appearance with the fosfomycin sachet. A mandarin and / or orange juice flavour plus sweetener was used. Was the placebo sachet also matched for taste?

Sponsor's response

The placebo sachets used in studies US-MON-01, US-MON-02 and US-MON-03 are matched with fosfomycin sachets for both the appearance and the taste.

Evaluator's response

The evaluator is satisfied with the sponsor's response.

11.3.2. TGA Question 2

- In pivotal studies MON-US-01 and MON-US-02, why was it considered necessary to change from a one-tailed to a two-tailed 0.05 level of significance?

Sponsor's response

The selection of a two-tailed test in the comparison of two drugs (no placebo) is more appropriate vs the one-tailed test because this can consider the hypothesis of superiority of any of the two drugs (trt A > trt B and trt B > trt A) and not only one (trt A > trt B or trt B > trt A). To be more conservative, the sample size was increased.

Evaluator's response

The evaluator is satisfied with the sponsor's response.

11.3.3. TGA Question 3

- In study MON-US-01, recurrence rates for fosfomycin were higher than for ciprofloxacin. Could the Sponsor provide the results of the susceptibility testing for ciprofloxacin and fosfomycin for the recurrent isolates? Did the recurrent isolates develop resistance to the study drug?

Sponsor's response

The data on susceptibility testing for ciprofloxacin and fosfomycin for the recurrent isolates are not available to the Sponsor. This test was not foreseen in the study protocol. However, data from literature showed that fosfomycin has a higher susceptibility compared to ciprofloxacin in *E.coli* isolate phenotype(s), including ESBL-producing (Karlowsky, 2014).

Evaluator's response

The evaluator is satisfied with the sponsor's response.

11.3.4. TGA Question 4

- For study MON-US-02, could the Sponsor provide the results of the susceptibility testing for fosfomycin and TMP/SMX for the recurrent isolates? Did the recurrent isolates develop resistance to the study drug?

Sponsor's response

The data on susceptibility testing for TMP/SMX and fosfomycin for the recurrent isolates are not available to the Sponsor. This test was not foreseen in the study protocol. Based on the current available data, the resistance rate to TMP/SMX or trimethoprim in Australia is 23.1%. It was evaluated in 5333 outpatient urinary isolates of E.coli (the most common urinary pathogen). The Australian authors reported a significant ($p<0.05$) increase in resistance over the five years of the study to trimethoprim (and TMP/SMX) (Fasugba, 2016).

Based on a recent analysis-report, it was shown that the resistance rates with TMP/SMX and other antibiotic agents are similar between Australia and Canada. The report states that the lowest resistance rate in Canada was with fosfomycin with a resistance rate of 0.1%.

The report further states that fosfomycin oral 3 g single dose is recommended as a first line therapy for uncomplicated urinary cystitis in the clinical practice guidelines in Canada, Europe and the US.

Evaluator's response

The evaluator is satisfied with the sponsor's response.

11.3.5. TGA Question 5

- In Studies MON-US-01, MON-US-02 and MON-US-03, are p values available for the comparison between the comparator antibiotic and fosfomycin for bacteriological efficacy against *E coli*?

Sponsor's response

The p values for the comparison of the efficacy between fosfomycin trometamol and comparators in the pivotal studies are not available to the Sponsor. Recently Falagas at al. (2010)1 and Grigoryan et al. (2014) performed an assessment of all fosfomycin clinical trials for UTI and reported that fosfomycin had a similar clinical efficacy (not-different) to other therapies (i.e. TMP/SMX, Nitrofurantoin, Fluoroquinolones and β- lactams). Fosfomycin 3 g single dose was deemed an appropriate first-line antibiotic for uncomplicated UTI treatment and a valuable treatment option.

Evaluator's response

The evaluator is satisfied with the sponsor's response. It is noted in the paper by Grigoryan et al (2014) that of the three first-line recommended therapies for acute uncomplicated lower UTI in the United States, 3g fosfomycin single dose had comparable clinical cure to trimethoprim / sulphamethoxazole DS 1 twice-daily for 3-7 days and also nitrofurantoin 200 mg in 2-4 divided doses for 5-7 days (all 91-92% clinical efficacy). However, the early bacterial cure of fosfomycin was 83% which was lower than nitrofurantoin (87%) and TMP/SMX (91%).

11.3.6. TGA Question 6

- Study US-MON-03 contains the following information: “In its evaluation of the efficacy of FT in the MON-US-01 and MON-US-02 trials, the FDA presented results to an Advisory Committee based on criteria which differed in certain respects from those defined prospectively in the protocols. Primarily, the FDA included the use of antibiotics for UTI as a criterion for failure and data from patients with "missing" visits were handled either by excluding the patient from the modified ITT analysis (for non-completers who discontinued for reasons other than treatment failure or related reasons) or by assigning outcomes on a case-by-case basis (for non-completers who remained in the modified ITT population because their discontinuation reason was related to treatment failure.)” Is the Sponsor able to provide the full transcript of the FDA report and also the statistical repeat analysis done according to the FDA recommendations?

Sponsor's response

The Sponsor does not have the full transcript and the repeated statistical analysis available. The Sponsor would like to point out that the abovementioned studies were performed in the early 1990s and retrieving such information/data older than 20 years was not feasible.

Evaluator's response

The evaluator is satisfied with the sponsor's response.

11.3.7. TGA Question 7

- The 3 pivotal studies MON-US-01, MON-US-02 or MON-US-03 do not contain much data on antimicrobial susceptibility testing results after therapy and whether resistance development occurred to the study drug. There is some individual patient data in MON-US-03 but is difficult to tease out and appears incomplete. Of particular importance is MON-US-01 which showed a significantly higher recurrence rate for fosfomycin patients compared to ciprofloxacin patients (14% versus 4%, $p<0.01$). Is the Sponsor able to provide any further antimicrobial resistance data for any of the 3 studies in early and late follow-up urine cultures after therapy?

Sponsor's response

The data on susceptibility testing for ciprofloxacin and fosfomycin for the recurrent isolates are not available to the Sponsor. This test was not foreseen in the study protocol.

Evaluator's response

The evaluator is satisfied with the sponsor's response.

11.3.8. TGA Question 8

- In PSUR Jan 1995-Dec 1999, the publication by Licciardello and Bignamini on the efficacy and safety of fosfomycin is missing all Figures. Could the Sponsor provide the full paper including all Figures please?

Sponsor's response

The full Licciardello and Bignamini, 1998 paper including the figures is provided as an addendum to PSUR Jan 1995-Dec 1999.

Evaluator's response

The evaluator is satisfied with the sponsor's response. No additional information of importance after review of complete paper.

11.4. Safety

11.4.1. TGA Question 1

- In pivotal study Mon-US-03, eosinophilia is reported in 57/362 (15.7%) of fosfomycin patients and 58/346 (16.8%) of nitrofurantoin patients (US-MON-03 report in the dossier). These are extraordinarily high results for both drugs. However, on review of the specific listing for eosinophilia, 20 (5.3%) fosfomycin patients and 14 (3.7%) nitrofuranotin patients appear to have had eosinophilia. This is still higher and out of keeping with studies MON-US-01 and Mon-US-02 in which eosinophilia rates were <1%. Could the Sponsor please advise the correct rates for eosinophilia for both study drugs? If the rates are till much higher than for fosfomycin in MON-US-01 and MON-US-02, could the Sponsor explain why? Was the formulation changed? Was any eosinophilia clinically significant?

Sponsor's response

The difference of percentage is probably due to a review of the data by the FDA that decided to underline the change of eosinophilia values from baseline to final in some patients even if some final values were not markedly clinically significant (>10.0), but an evident difference between the two compared values. Based on the analysis of the documentation available on the pivotal studies, the sponsor was not able to retrieve information about the different eosinophilia rates observed in MON-US-03 and in the other 2 pivotal studies.

Evaluator's response

The evaluator is satisfied with the sponsor's response. Eosinophilia is likely artificially high in both fosfomycin and comparator arm due to altered definition of eosinophilia. Eosinophilia is not likely to be clinically significant.

11.4.2. TGA Question 2

- This information is contained in PSUR Jan 2005-Aug 2009 PSUR p11. Zambon Nederland B.V in 2008 changed the safety warning in the PI. Information on sucrose content in the formulation has been updated with the following sentence: “This medicinal product contains sucrose. Patients with rare hereditary diseases as fructose intolerance, glucose-galactose malabsorption or deficiency of sucrase-isomaltase should not use this product”. This warning is also included in the proposed Australian PI. Presumably this safety warning has been added because each sachet of Monurol contains more than 2g sucrose which patients with the hereditary deficiencies cannot metabolise. Is this the case? If so, what adverse events have been noted in these patients? Or is it a theoretical risk only? Does the sucrose load alter serum glucose levels in diabetes mellitus?

Sponsor's response

Since the medicinal product contains 2.213 g sucrose per sachet, its use in the event of fructose intolerance, glucose or galactose malabsorption syndrome or sucrase-isomaltase deficiency is not recommended. The sentence “This medicinal product contains sucrose. Patients with rare hereditary diseases as fructose intolerance, glucose-galactose malabsorption or deficiency of sucrase-isomaltase should not use this product” was added according to the guideline Guidelines Medicinal products for human use Safety, environment and information - Excipients in the label and package leaflet of medicinal products for human use (July 2003)

Evaluator's response

The evaluator is satisfied with the sponsor's response.

11.4.3. TGA Question 3

- Is the Sponsor aware of any safety issues in patients with hereditary abnormalities of sugar metabolism or G6PD deficiency?

Sponsor's response

A search of the Company's worldwide database of all cases that have been cumulatively collected up to 31 Dec 2016, did not reveal any case reporting as Medical History a condition mapping to SMQ Congenital, familial and genetic disorders and describing hereditary abnormalities of sugar metabolism or G6PD deficiency.

Evaluator's response

The evaluator is satisfied with the sponsor's response.

11.4.4. TGA Question 4

- The proposed PI includes the following wording, under section "Overdose": "The following events have been observed in patients who have taken Monurol in overdose: vestibular loss, impaired hearing, metallic taste, and general decline in taste perception. In the event of overdosage, treatment should be symptomatic and supportive. Rehydration is recommended to promote urinary elimination of the drug." Could the Sponsor advise the source of the comments on taste alteration?

Sponsor's response

The text originated from the label approved by the FDA for Monurol in the US and this text has also been proposed for the Australian PI. The reported event i.e. general decline in taste perception has been described in two case reports in pattern of overdose (i.e. with a length of treatment with fosfomycin trometamol above the locally approved maximum recommended dose).

Cumulatively up to 31 Dec 2016, one additional serious report and eight nonserious spontaneous reports of dysgeusia were received at therapeutic doses. In addition, there was one non-serious case of hypogeusia and one of ageusia for which no information about fosfomycin dosage, was collected.

Evaluator's response

The evaluator is satisfied with the sponsor's response.

11.5. RMP

Responses to RMP evaluation are to be principally assessed by the Post-market Branch of TGA. My comments as clinical evaluator are as follows:

11.5.1. TGA Recommendation 1

- Any safety concerns identified by the Clinical or Nonclinical Evaluators that impact on the safety specifications should be addressed in a revised RMP.

Sponsor's response

The sponsor has reviewed the Clinical and Non-Clinical Evaluator's reports and taking into account our s31 responses, we did not identify any safety concerns that impact the safety specifications and therefore a revision to the previously provided RMP document is not required.

Evaluator's response

There are some minor changes in the draft RMP, v1.2, April 2017 compared to v1.1, July 2016. These were largely in response to the clinical evaluator and non-clinical evaluators' questions and concerns. The evaluator is satisfied with the sponsor's response.

11.5.2. TGA Recommendation 2

· The bacterial resistance surveillance program should be identified as an additional pharmacovigilance activity in future revision of the ASA.

Sponsor's response

The ASA has been updated to clearly specify that the bacterial resistance surveillance program is an additional PV activity. Furthermore, the updated ASA version 1.2 has been updated to reflect the changes made to the PI (version 0.3).

Evaluator's response

The evaluator is satisfied with the sponsor's response.

11.5.3. TGA Recommendation 3

· With regards to resistance surveillance, it is recommended that the sponsor investigate options for using national level resistance data from initiatives such as AURA (Antimicrobial Use and Resistance in Australia).

Sponsor's response

Discussion with AURA has clarified that AURA does not perform any isolate testing. AURA is involved in analyses and the reporting of information from data sources such as Australian Group on Antimicrobial Resistance (AGAR), some national data (NPS MedicineWise, PBS/RPBS), hospital or community testing sites.

Currently, fosfomycin is not readily available in the Australian market and as such, susceptibility testing is not actively performed. Furthermore, fosfomycin is not included in the current Australian testing panels for the most commonly used automated susceptibility testing systems in Australia (Vitek 2).

The available local fosfomycin resistance data to date (via Special Access Scheme supply) are generated by a select few Australian hospitals for complicated infections.

The sponsor therefore, believes the proposed targeted post-marketing surveillance program – which incorporates both an active and passive component would be better led and analysed by a co-ordinating body such as AGAR, which is familiar with isolate test methodologies and has access to a range of suitable participating laboratories nationally. Also, it has the capacity to store isolates and perform any additional testing on site if required, thus collecting the required targeted post-marketing resistance surveillance data for uncomplicated urinary tract infections.

Furthermore, the sponsor intends to the share the annual post marketing surveillance program report with AURA; thus, further contributing to national data collection and analysis for Australia. The ASA has been updated to reflect this voluntarily data sharing proposal as part of its local risk minimisation plan (see updated ASA version 1.2).

Evaluator's response

The clinical evaluator agrees that AGAR is the most appropriate group in Australia to collect and record fosfomycin susceptibility data post-marketing. It is agreed that at the present time there is extremely limited fosfomycin susceptibility data due to limited largely hospital-based usage for complicated and uncomplicated UTI, often caused by bacteria resistant to other antibiotics.

Approval of the drug is likely to result in its inclusion in automated susceptibility testing systems such as Vitek 2 so that data will be easily available. EUCAST in 2017 has also added disc

susceptibility breakpoints for E coli only in uncomplicated lower UTI (S >24 mm), with other Enterobacteriaceae still requiring MIC testing.

11.5.4. TGA Recommendation 4

- The sponsor is requested to respond to the off-label use concerns of the Clinical Evaluator, being that 'the potential for off label use is high in the treatment of UTIs caused by ESBL-producing beta-lactamases or carbapenemases…' The sponsor should provide comment on whether additional risk minimisation is required to mitigate the risk of such off-label use.

Sponsor's response

The in-label/off-label use of fosfomycin trometamol is linked to the clinical indication (i.e. uncomplicated UTIs) and not to bacterial strains. Thus, therapy of (fosfomycin susceptible) ESBL or carbapenemase harbouring isolates may be entirely appropriate. This may also avoid the need for parenteral therapy where no other oral option is available.

The Australian PI clearly states:

Monurol is not indicated for the treatment of pyelonephritis or perinephric abscess.

The sponsors also note that nitrofurantoin occupies a somewhat similar therapeutic position. This agent is indicated only for the therapy of lower urinary tract infection. Additionally, a number of ESBL and/or Carbapenemase harbouring bacteria maintain susceptibility to this agent. To the best of our knowledge this has not led to significant reports of inappropriate off-label use.

Evaluator's response

The evaluator is satisfied with the sponsor's response.

11.5.5. TGA Recommendation 5

- The sponsor should provide comment on the potential risk of Monurol® being administered off-label in Australia with adjusted paediatric dosing given the paediatric 2 g sachet available overseas is not included in this application.

Sponsor's response

The peak age for cystitis for women is reported to be in the 25-34 and 35-54 age groups, with a decreased rate in women aged 55-74 years and a rising prevalence in women aged over 75 years. In light of the above, the risk of off-label use in paediatric population can be considered very low.

Evaluator's response

The evaluator is satisfied with the sponsor's response.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

After consideration of the responses to the clinical questions, the benefits of fosfomycin trometamol (Monurol) in the proposed usage are unchanged from those identified above apart from the issue of the potential for off-label usage of the drug in ESBL-producing or carbapenemase-producing Gram negatives. Provided that the organism is fosfomycin-susceptible and the UTI is acute and uncomplicated, single-dose fosfomycin is an appropriate choice for therapy in these patients. The evaluator reiterates that the correct dosing schedule for the drug in complicated UTI is unknown so in this condition the drug should not be used. The evaluator encourages the sponsor to undertake further clinical studies which include serum

and urinary level monitoring in patients with complicated UTI (not pyelonephritis or perinephric abscess).

12.2. Second round assessment of risks

After consideration of the responses to the clinical questions, the risks of Monurol in the proposed usage are unchanged from those identified above, apart from the following points.

- Single dose Monurol has good clinical and bacteriological efficacy in the treatment of acute uncomplicated UTI, comparable to 7 days of nitrofurantoin. However, it has acceptable but lower bacteriological efficacy than 7-10 days of ciprofloxacin or TMP/SMX. Hence like all other single dose antibiotic therapies,[29] single dose Monurol should not be used in as a single dose in pregnancy and the PI should reflect this.
- Using EUCAST or CLSI guidelines (the common susceptibility testing methods in Australia), susceptibility testing for Monurol is only calibrated for Enterobacteriaceae (including E. coli) and Enterococcus faecalis. Also, some enterococci and some species of Enterobactericeae (for example Enterobacter spp, Serratia, Morganella) are frequently resistant. Staph saphrophyticus, a common pathogen in community-acquired UTI, can be quite resistant, when breakpoints are extrapolated from E. faecalis. Pseudomonas is frequently resistant to fosfomycin; in vitro mutants arise more readily after exposure than for E. coli and some studies suggest that unlike E. coli there is no biological cost associated with the development of fosfomycin resistant mutants in Pseudomonas (Karageorgopoulos et al, 2012).[30] Hence, the evaluator recommends that the proposed indication for acute uncomplicated lower UTI be narrowed to the treatment of acute uncomplicated lower UTI caused by susceptible strains of Enterobacteriaceae (including Escherichia coli) and Enterococcus faecalis.

  The evaluator notes that the PIs in countries who have most recently approved fosfomycin, for example USA (1996) and Canada (1999) have limited the approval to the pathogens E. coli and E. faecalis. This may in part reflect the predominance of CLSI as the susceptibility testing method most commonly used in those countries. Using CLSI methodology, E. coli and E. faecalis are the only urinary pathogens calibarated for fosfomycin susceptibility testing. However, given that EUCAST since 2013 has had susceptibility testing guidelines for other Enterobacteriaceae apart from E. coli, and that based on pivotal trial data, fosfomycin is likely to be efficacious in fosfomycin-susceptible Enterobacteriaceae apart from E. coli, species approval does not need to be limited to E. coli but can encompass the other Enterobacteriaceae.
- Fosfomycin-resistant mutants of bacterial species including E. coli occur relatively frequently following therapy but the biological fitness of these mutants apart from possibly Pseudomonas appears lowered (see Karageorgopoulos, 2012).[31] In Europe and other countries with high historical fosfomycin usage, fosfomycin susceptibility has been preserved apart from a few resistant clones. The post-marketing surveillance RMP proposed (v1.2, April 2017) with the assistance of AGAR will be important to monitor resistance development.
- The relative place of fosfomycin in the treatment of acute uncomplicated UTI needs consideration. Therapeutic Guidelines: Antibiotic[32] is the appropriate Australian expert

[29] Therapeutic Guidelines: Antibiotic v14.
[30] Karageorgopoulos DE, et al. Fosfomycin: evaluation of the published evidence on the emergence of antimicrobial resistance in Gram-negative pathogens. J Antimicrob Chemother. 2012 Feb;67(2):255-68.
[31] Karageorgopoulos DE, et al. Fosfomycin: evaluation of the published evidence on the emergence of antimicrobial resistance in Gram-negative pathogens. J Antimicrob Chemother. 2012 Feb;67(2):255-68.
[32] Therapeutic Guidelines: Antibiotic v14.

body to do this, taking into account efficacy compared to other agents, cost, convenience, potential for antimicrobial resistance and the threshold for acceptability of clinical failure.

- The paper by Falagas[33] included by the sponsor states:

  Fosfomycin may increase the levels or effects of digoxin; patients should be monitored closely when digoxin and fosfomycin are coadminstered. A low risk for contraceptive failure exists when fosfomycin is coadministered with conjugated estrogens… Finally, fosfomycin trometamol should not be coadministered with probenecid which decreases renal clearance and excretion of fosfomycin (Paladin Labs, 2007, Monurol package insert, Canada).

  Could the sponsor please advise whether there are clinically significant interactions of fosfomycin with digoxin, conjugated estrogens and / or probenecid? If so, statements will need to be added to the PI.

- In post-marketing surveillance, 5 cases of increased or decreased INR were noted. In the second round, the sponsor has added a comment to the draft PI "Effects on laboratory tests" regarding alteration in INR. Is the sponsor able to provide more information on these 5 cases, specifically regarding possible interactions with anticoagulants?

- The nonclinical evaluator has noted that fosfomycin is most bactericidal at typical urinary pH.[34] Also, development of mutational resistance could be less at acid pH).[35] If this is correct, concomitant urinary alkalinisers would not be recommended. A statement has been added to the draft PI regarding this.

- The evaluator has reviewed the PI justification document in the response presented by the sponsor in the second round. In this document, the sponsor has requested that the following events be excluded from the PI: aplastic anemia, cholestatic jaundice, hepatic necrosis, toxic skin eruptions, and toxic megacolon. These events were requested for inclusion by the evaluator and are all included in the current US PI dated 2 Feb 2011 submitted by the sponsor in round 1.

12.2.1. Toxic megacolon

Gastointestinal disorders

The sponsor has advised in the PI justification document in the response that toxic megacolon has never been reported, but toxic megacolon is listed in the post marketing experience section of the US PI dated 2 Feb 2011. Could the sponsor advise the source of the listing in the US PI, as toxic megacolon may be included as an adverse event of “not known: frequency” category?

Aplastic anaemia

One case noted:

- PSUR 1 Jan 1995 - 31 Dec 1999. A patient with small cell lung cancer developed fatigue and was noted to have aplastic anaemia on bone marrow biopsy. This occurred about 2 weeks after single dose of fosfomycin with itraconazole 1g daily g for 6 days started on the same day. Patient also received ciprofloxacin and fluconazole the same week. The patient died about 4 weeks after bone marrow biopsy with unknown cause of death.

This case is also described in more detail in the PI justification document in the response received in the second round. The evaluator agrees with the sponsor that aplastic anaemia is

[33] Falagas ME, et al. Fosfomycin. Clin Microbiol Rev. 2016 Apr;29(2):321-47.
[34] Wise R, Andrews JM (1987). Fosfomycin trometamol: an in vitro study. New Trends in Urinary Tract Infections. Neu, Williams (eds.), 224–231.
[35] Karageorgopoulos DE, et al. Fosfomycin: evaluation of the published evidence on the emergence of antimicrobial resistance in Gram-negative pathogens. J Antimicrob Chemother. 2012 Feb;67(2):255-68.

unlikely due to fosfomycin based on the information provided. However, the US PI dated 2 Feb 2011 lists aplastic anaemia in the post-marketing experience section. Could the sponsor advise details of this post-marketing report? Is it based on the case in question or on additional cases? The evaluator agrees that this case in the PI justification document in the response is not assessable. If there are no other cases, recommend aplastic anaemia is not included as an adverse event in the PI.

Toxic skin eruption

Three cases of toxic skin eruption and 44 cases of severe cutaneous adverse events were noted, based on post-marketing reports:

- PSUR 1 Jan 2005 - 31 Aug 2009. Toxic skin eruption requiring 7 days hospitalisation. Resolved.
- PSUR 1 Jan 2005 - 31 Aug 2009. Toxic skin eruption starting 24 h after fosfomycin. Resolved.
- PSUR 1 June 2009 - 31 Nov 2009. Toxic skin eruption and fever starting 24 h after fosfomycin, lansoprazole and trimebutine. Resolved.
- PSUR 1 June 2010 - 31 May 2015. 44 cases. Severe cutaneous adverse reactions.

In post marketing surveillance, the following severe skin reactions were noted: erythema multiforme (2 cases), Stevens-Johnson syndrome (1 case), drug reaction with eosinophilia and systemic symptoms (2 cases) and toxic epidermal necrolysis (2 cases).

Based on this information, recommend listing "Unknown frequency: toxic skin eruption" under the skin and subcutaneous tissue disorders heading. Recommend also advice from the TGA delegate and / or a dermatologist as to whether "toxic skin eruption" is the best and most appropriate current dermatological summary wording to encompass the serious skin reactions reported.

Cholestatic jaundice, hepatic necrosis

The evaluator has reviewed the additional cases in the PI justification document. There are sufficient cases of liver injury temporally associated with fosfomycin without other cause to recommend listing as follows:

- Gastrointestinal disorders: "Not known: cholestatic hepatitis, toxic hepatic necrosis".

It is also noted that cholestatic jaundice, hepatic necrosis are listed in the post-marketing experience section of the US Product Information dated 2 Feb 2011.

12.3. Second round assessment of benefit-risk balance

The benefit-risk balance of Monurol, given the proposed usage, is favourable, provided the Sponsor provides a satisfactory response to the questions and issues discussed above.

13. Second round recommendation regarding authorisation

Subject to the sponsor's satisfactory response to the questions and issues raised, approval of Monurol (fosfomycin tromethamine) is recommended subject to narrowing of the indication to read as follows (note changes required are in **bold font**):

> *Monurol is indicated only for the treatment of acute uncomplicated lower urinary tract infections (acute cystitis) in women above 12 years of age* ***caused by the following susceptible pathogens: Enterobacteriaceae (including Escherichia coli), Enterococcus faecalis.***

The reasons for narrowing the indication have been discussed in detail above, and also in the first round review, particularly Pharmacodynamics.

14. References

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